





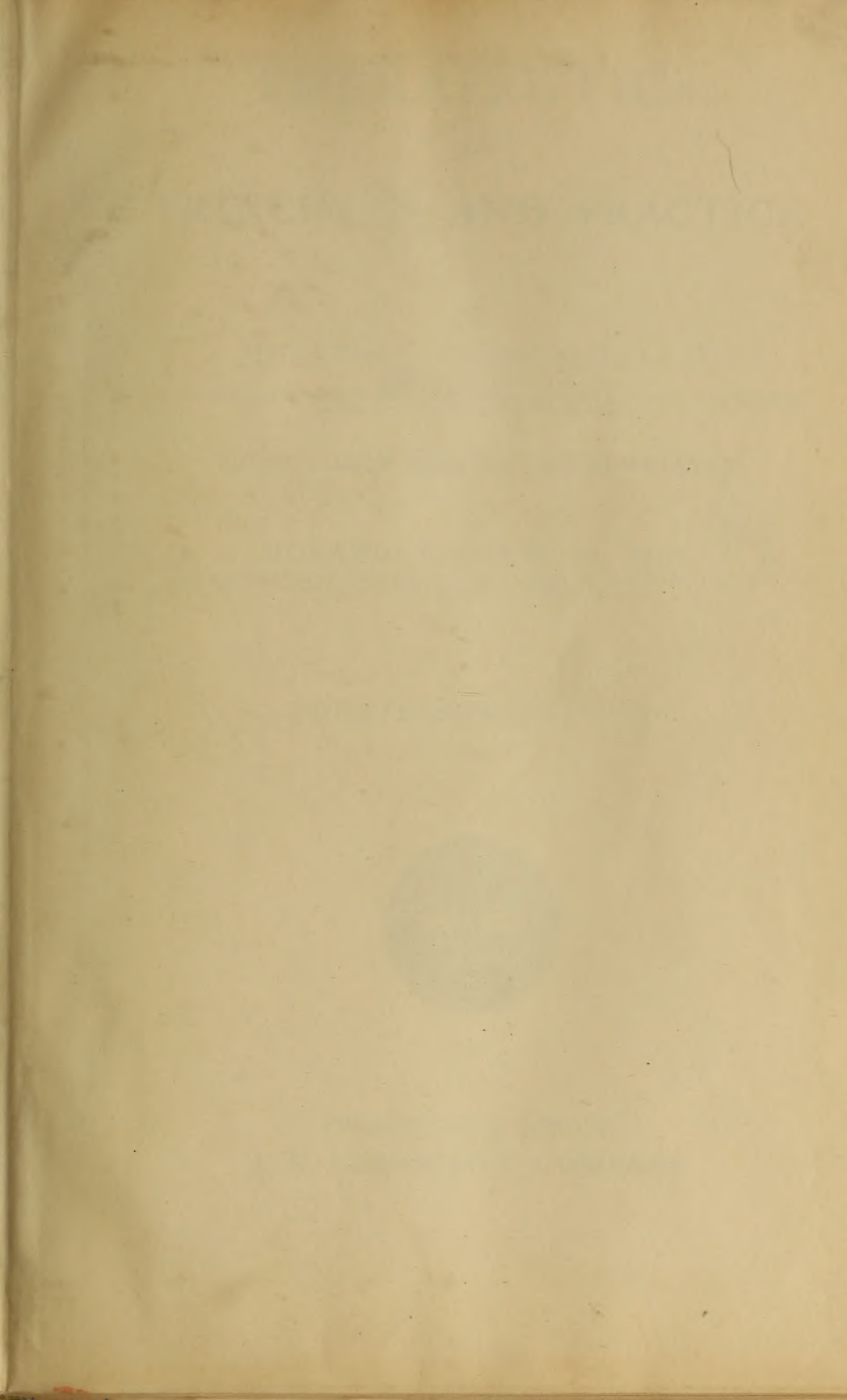
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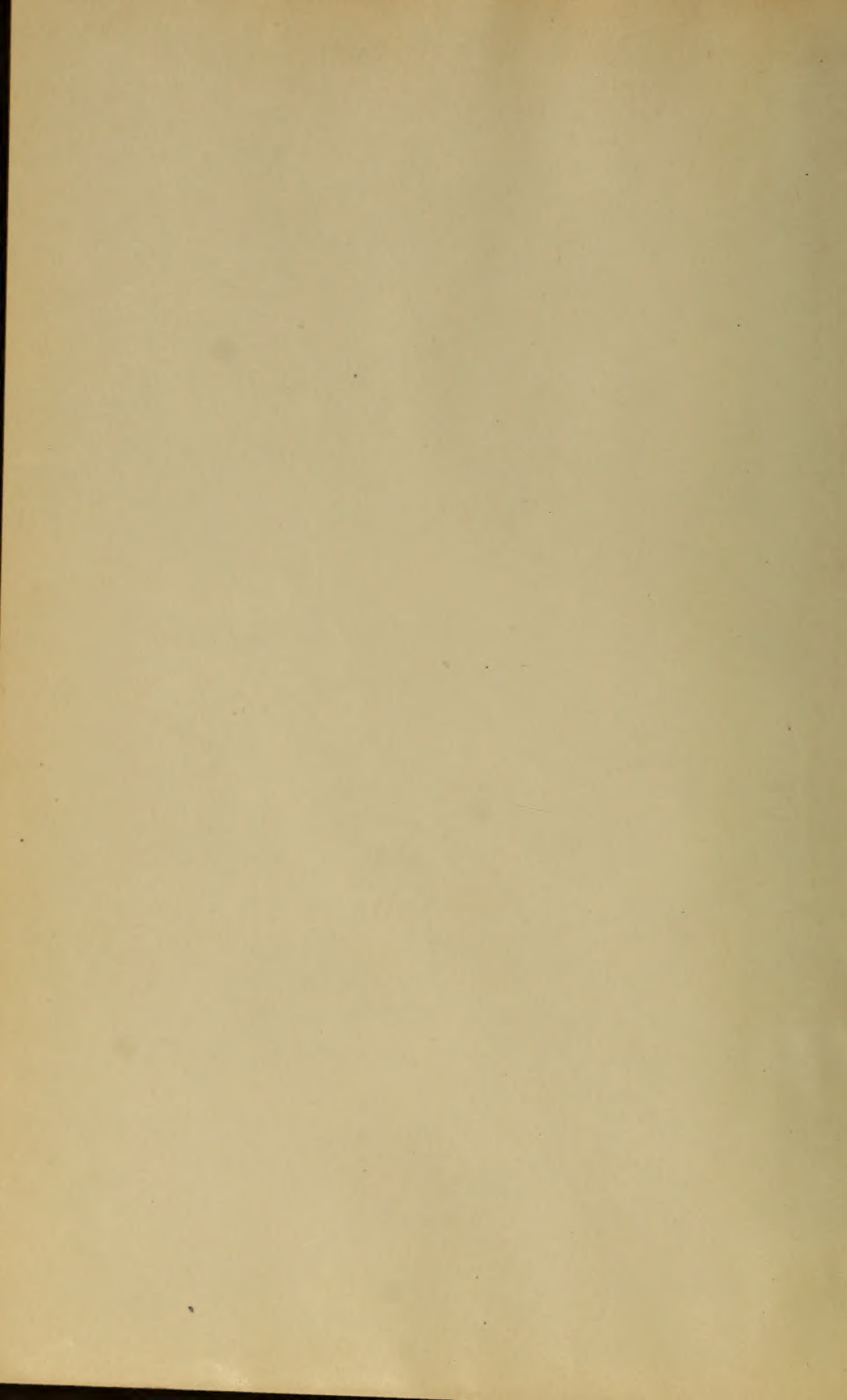
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# THERAPEUTICS:

ITS

## PRINCIPLES AND PRACTICE

BY

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FOURTEENTH EDITION



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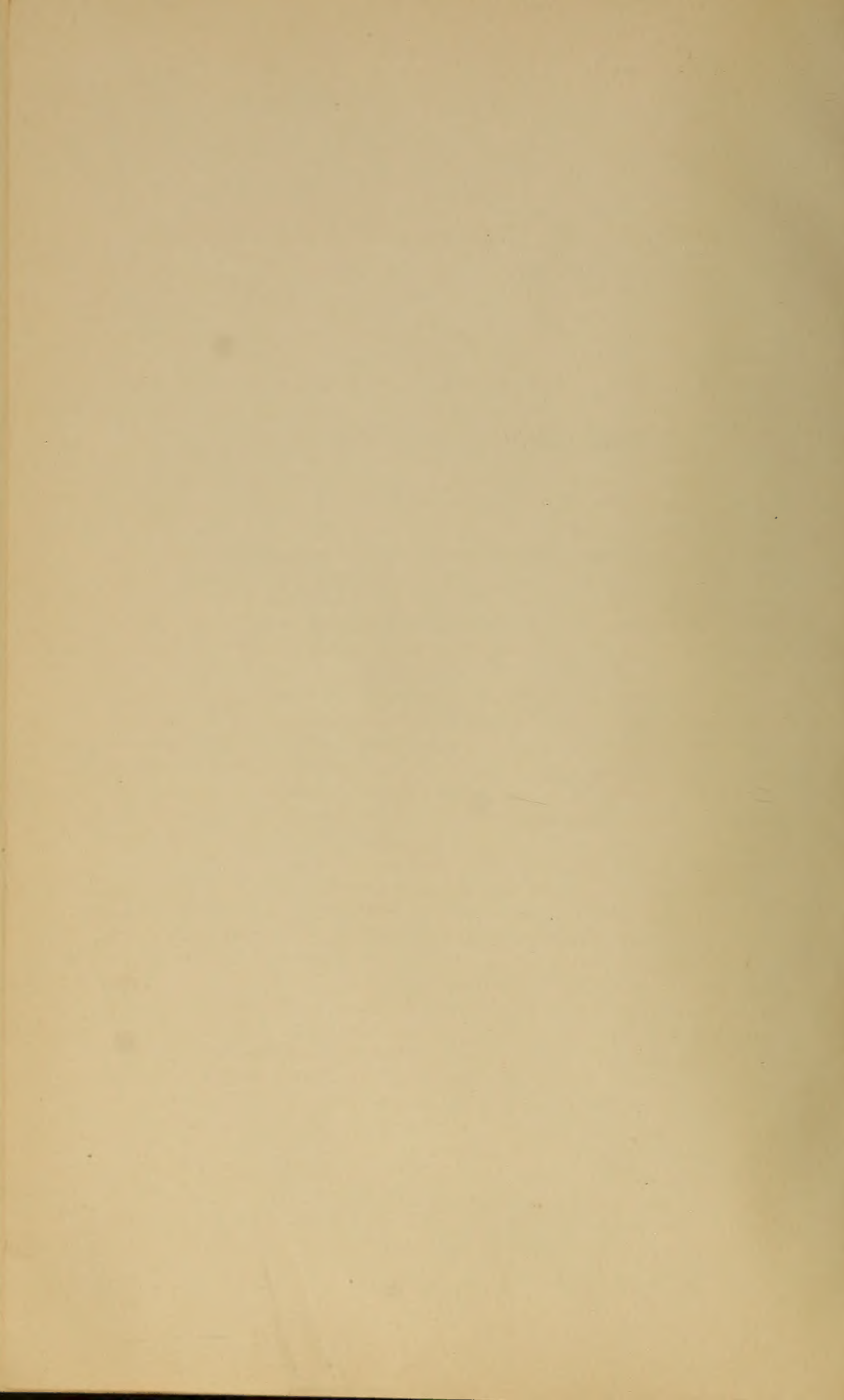
DR. GEORGE B. WOOD, LL.D.,

THIS BOOK

IS DEDICATED BY THE AUTHOR, HIS NEPHEW,

AS A TOKEN OF RESPECT AND

AFFECTION.



## PREFACE TO THE FOURTEENTH EDITION

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THE alterations in the present edition of this treatise are more extensive than those in any previous edition for many years. Many of these changes are the result of an effort to make the book more available as a student's text-book without lessening its value as a work of reference for the practitioner or scientist.

The fundamental facts which the undergraduate student should be required to know are printed in large type, while the discussion of the more intricate details of pharmacology and the therapeutic data of less importance are printed in smaller type. The descriptions of the physical characteristics of the drugs at the beginning of each article have been carefully revised, and enlarged where deemed necessary, so that, although the book does not pretend to give a detailed treatise on *materia medica*, it is believed that it contains the facts on this subject which the practitioner of medicine should know.

Besides the more systematic arrangement of the subject-matter and the changes above noted a considerable amount of alteration has been required to keep the work abreast of the recent discoveries in the rapidly advancing science of pharmacology. The whole field of medical literature of the world has been sedulously gleaned and facts of therapeutic interest which have been found incorporated in the text. Especially notable changes, however, have been found necessary in the following portions of the work:

The chapter on cathartics has been completely rewritten and the matter considered in a more orderly manner, which we believe will be of advantage alike to the student and practitioner of medicine.

The chapter on diuretics has been remodelled to correspond to the latest views of the physiology and pharmacology of this subject, and more space given to the consideration of the effects of water on the system and the action of mineral salts on the flow of urine.

Articles on opsonic therapy and on the ion theory have been added. Also a number of new illustrations have been introduced where it was thought that they would elucidate the text; many of these are photographic reproductions of blood-pressure and respiratory curves from experiments made by the reviser.

Continued ill health has prevented the original author of this treatise from taking any active part in the present edition and the entire labor has fallen on his son, Dr. Horatio C. Wood, Jr., who has been associated in the various revisions of the work for the past eight years.





## PREFACE TO THE FIRST EDITION

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At the present time, when the shelves of private and public libraries are groaning beneath their ever-increasing loads, when a thousand presses in every city send forth day and night their printed messages until the earth is filled with them, it seems almost presumptuous for any one to offer new volumes to the world. Indeed, art is so long, life is so short, that every student has the right to demand of an author by what authority he doeth these things, and to challenge every memoir for its *raison d'être*. This being so, it assuredly will not appear egotistical for the author to state that his voluntary task was first suggested by his own wants, and that to its performance he has brought the training, labor, and experience of years spent in the laboratory, the study, the class-room, and the hospital ward.

There are a number of excellent treatises upon *materia medica* and therapeutics; yet in various attempts at original research, as well as in the ward and the lecture-room of the hospital, I have keenly felt the want of something more. There are many points of view from which a subject can be looked at; there are many paths by which it may be approached; and to me, other points of view, other modes of approach, have been far more enticing than those adopted in our standard treatises.

The old and tried method in therapeutics is that of empiricism, or, if the term sounds harsh, of clinical experience. As stated by one of its most ardent supporters, the best possible development of this plan of investigation is to be found in a close and careful analysis of cases before and after the administration of a remedy, and, if the results be favorable, the continued use of the drug in similar cases. It is evident that this is not a new path, but a highway already worn with the eager but weary feet of the profession for two thousand years.

That very much has been thus accomplished it were folly to deny. Leaving out of sight the growth of the last two decades, almost all of the current therapeutic knowledge has been gained in this way.

Therapeutics developed in this manner cannot, however, rest upon a secure foundation. What to-day is believed is to-morrow to be cast aside, certainly has been the law of advancement, and seemingly must continue to be so. What has clinical therapeutics established permanently and indisputably? Scarcely anything beyond the primary facts that quinia will arrest an intermittent, that salts will purge, and that opium will quiet pain and lull to sleep.

To established therapeutic facts the profession clings as with the heart and hand of one man,—clings with a desperation and unanimity whose intensity is the measure of the unsatisfied desire

for something fixed. Yet with what a Babel of discordant voices does it celebrate its two thousand years of experience!

This is so well known that it seems superfluous to cite examples of the therapeutic discord; and one only shall be mentioned,—namely, rheumatism. In this disease, bleeding, nitrate of potassium, quinine, mercurials, flying blisters, purgation, opium, the bromides, veratria, and a host of other remedies, all have their advocates clamorous for a hearing; and above all the tumult are to be heard the trumpet-tones of a Chambers, “Wrap your patients in blankets and let them alone.”

Experience is said to be the mother of wisdom. Verily she has been in medicine rather a blind leader of the blind; and the history of medical progress is a history of men groping in the darkness, finding seeming gems of truth one after another, only in a few minutes to cast each back to the vast heap of forgotten baubles that in their day had also been mistaken for verities. In the past, there is scarcely a conceivable absurdity that men have not tested by experience and for a time found to be the thing desired; in the present, homœopathy and other similar delusions are eagerly embraced and honestly believed in by men who rest their faith upon experience.

Narrowing our gaze to the regular profession and to a few decades, what do we see? Experience teaching that not to bleed a man suffering from pneumonia is to consign him to an unopened grave, and experience teaching that to bleed a man suffering from pneumonia is to consign him to a grave never opened by nature. Looking at the revolutions and contradictions of the past,—listening to the therapeutic Babel of the present,—is it a wonder that men should take refuge in nihilism, and, like the lotus-eaters, dream that all alike is folly,—that rest and quiet and calm are the only human fruition?

Since the profession has toiled so long and found so little, if further progress is to be made we must question the old methods and search out new ones, which haply may lead to more fruitful fields. In the ordinary affairs and business of life, when anything is to be accomplished, the effort always is to discover what is to be done, and then what are the means at command. A primary knowledge of the end to be accomplished, and a secondary acquaintance with the instruments, are a necessity for successful human effort; and until the sway of this law is acknowledged by physicians, medicine can never rise from the position of an empirical art to the dignity of applied science. Until within a comparatively recent period, it has been impossible to comply with this law. But, through the advances made by the pathologists and by the students of the natural history of disease, we are fast learning the methods in which nature brings the body back to health. When this is done,—when disease is thoroughly understood,—we shall have wrought out the first element of the problem, shall have complied with the first requirement of the law.

It is scarcely within the province of a therapist, and certainly is not possible within the scope and limits of this work, to discuss at

length the natural history of disease; but it is allowable to point out evident indications for relief; and this I have done to a greater or less extent throughout the book.

The work of the therapist is chiefly with the second portion of the law. Evidently, it is his especial province to find out what are the means at command, what the individual drugs in use do when put into a human system. It is seemingly self-evident that the physiological action of a remedy can never be made out by a study of its use in disease. Under all circumstances, the problem is one of the most complex with which the human mind has to grapple; and to introduce into this problem the new and ever-varying factors of the effect of disease and its natural vibrations on the system is to put the matter beyond human prescience.

In spite, then, of Dr. Niemeyer's assertion that experiments made with medicaments upon the lower animals or upon healthy human beings have, as yet, been of no direct service to our means of treating disease, and that a continuation of such experiments gives no prospect of such service, it is certain that in these experiments is the only rational scientific groundwork for the treatment of disease. We must discover what influence a drug exerts when put into the body of a patient before we can use it rationally; and we can gain this coveted knowledge only in the method indicated.

It has been strenuously objected, especially to experiments upon animals, that drugs do not act upon the lower creatures in the same manner as they do upon man. When I first commenced the studies whose outcome is the present volume, I was profoundly impressed with the truth of this oft-repeated assertion and with the difficulties which it put in the way. To-day I do not believe that, stated in its broad sense, it is true. Indeed, more strongly, I assert that it is not true; that, in the vast majority of cases, the actions of drugs upon man and upon the lower animals are, though seemingly different, in reality similar; that the more knowledge we acquire the fewer exceptions remain unexplained; and that the whole matter is in all probability subject to laws whose development will greatly aid in our explanation of various obscure clinical phenomena.

The general proofs of these assertions are sufficiently obvious, I think, in the following pages to render it unnecessary for me to dwell upon them at length here: moreover, if they be not so obvious to others as to myself, space is here wanting for a full discussion of the subject. I can only make a few general remarks, and point out some of what I believe to be the governing laws.

In the first place, degree and quality are distinct things, and should not be confounded. Yet they frequently are; and because it requires as much morphia to kill a pigeon of a pound weight as to destroy a man, we are told that medicines act differently upon man and the lower animals. Evidently the conclusion is a *non sequitur*, and difference of susceptibility is no proof of difference in the mode of impression. A teaspoonful of Epsom salt may purge one man, while it may



require ounces to affect another. Evidently there is a difference of susceptibility; but when the impression is once made it is of the same character in each case. As with man and man, so with man and the pigeon,—susceptibility is no measure or gauge of the character of the impression.

A large number of drugs—indeed, it may be said, the larger number of important drugs—exert in the system antagonistic actions. Thus, atropia stimulates the spinal cord, but destroys the conducting power of the nerve-trunks. It is evident that as one or other of these influences predominates, will there be convulsions or paralysis. Now if for any reason one animal be exceedingly sensitive to the spinal action of atropia, that animal will in belladonna-poisoning suffer from convulsions, while its fellow, which is affected chiefly by the nerve-action of the drug, will, under like circumstances, have paralysis. Here the mere clinician, with his superficial knowledge, seeing the paralyzed and the convulsed lying side by side, says, What a hopeless muddle! Poor fools, these vivisectors! they will never come to any good! In truth, the differences in symptoms in these and in many other cases simply depend upon differences in susceptibility; and the only lesson that the circumstance teaches is the importance of discovering the laws which govern these susceptibilities.

A law which governs the susceptibility to the action of drugs is, that the more highly specialized any system is the more readily affected is it by a medicine. Thus, the cerebrum of a man is far more highly organized than that of any other animal, and consequently he is far more sensitive to the action of drugs which affect the cerebrum than are the lower forms. Again, in the frog the spinal system is especially developed,—probably, in proportion to the cerebrum, more so than in any other of the animals commonly experimented with: consequently the batrachian is excessively sensitive to remedies which, like strychnia, affect the spinal cord. In obedience to this law, we have resulting the action of opium,—an action which has been considered the strongest proof of the hopelessness of any attempt to explain the effects of drugs upon a man by experiments upon the lower animals. In man, opium causes deep stupor and general relaxation; in the frog, it causes tetanic convulsions. The explanation of these seeming inconsistencies is, however, very evident when the whole subject is looked at. Opium in all animals has a double action, one upon the cerebrum and one upon the spinal centres. In the frog, the latter being the more highly organized, the spinal action overcomes the cerebral; in man, the cerebrum being the more sensitive, stupor replaces the convulsions: yet in man convulsions sometimes occur in opium-poisoning, and in the frog the dose can be so managed as to cause stupor.

A second law which seems to hold sway over the action of drugs upon different animals is that great differences of function in a system affect its relation to drugs: thus, in an herbivorous animal the alimentary canal is very different from what it is in the carnivora,



whose digestive organs in turn differ from those of man,—the omnivore. Medicines which act upon the alimentary canal are apt to vary in their effects upon different orders of animals.

Converse to the above law is that which renders systems which are little specialized similarly acted upon by drugs in different classes of animals.

Thus, the general structure and the functions of the circulatory system are very uniform among vertebrates, as is also the action of those drugs which affect chiefly the circulation: thus, aconite, or digitalis, or potash, influences in the one way the heart of the frog, of the rabbit, and of man.

There are a very few apparent exceptions to the uniformity of the action of drugs upon all animals which seemingly contravene the laws that have been mentioned. These exceptions are so few, however, that without doubt advancing knowledge will by and by explain them all and show what are the laws which for the time being hold in abeyance or overcome those already stated.

An asserted fact which has recently been brought forward as revealing the worthlessness of animal experimentation is that some monkeys are not susceptible to the action of strychnia, while others are. Granting the truth of the asserted fact, it certainly is explainable. It is at least conceivable that a given species of animal may, by the gradually acquired habit of feeding upon a substance containing a narcotic poison, acquire an insusceptibility to the influence of that poison which shall as it were belong to its specific type, or, in other words, be an acquired specific character. The nervous system of the opium-eater becomes accustomed to the stimulant, and it is not impossible that a measure of the habit should be transmitted. If the Darwinian law of the gradual evolution by the survival of the fittest have any force, these curious apparent freaks of medicines in regard to their physiological action may be the result of this law, especially since it is species which are affected. It is not all monkeys that are proof against strychnia, but, as we are distinctly told, only one species of monkey; and, so far as I know, it is not all deer that are said to thrive when fed upon tobacco, but only the Virginia deer. Whether this conception be or be not a mere fancy, this much is to my mind very clear, that the few scattered exceptions ought not to outweigh the immense mass of evidence upon the other side, and that it is inconceivable that drugs, in their relations to animal organisms, differ from all other created things in not being subject to law.

In the early portion of this preface I stated that the work had grown out of a need felt by myself: that need was for a book into which should be gathered the many scattered facts in regard to the physiological action of medicine,—a book in which an attempt should be made to sift the true from the false, to reconcile seeming differences, to point out what we know and what we do not know, and to give a platform from which investigators might start forward without the necessity of being, as is so often the case, ignorant of what was already

achieved, or of spending a great deal of time in a wild hunt through the almost boundless, but often scattered and inaccessible, ranges of Continental literature.

The plan of the present work has been to make the physiological action of remedies the principal point in discussion. A thoroughly scientific treatise would in each article simply show what the drug does when put into a healthy man, and afterwards point out to what diseases or morbid processes such action is able to afford relief. Unfortunately, in the great majority of cases our knowledge is not complete enough for this, and the clinical method has to be used to supplement the scientific plan.

I have added to the book a consideration of toxicology, so far as it is of interest to the physician. This has been done for several reasons. First, it was necessary to study the action of poisonous drugs upon man, in order to make out their physiological action; secondly, physicians are constantly required to diagnose and to treat cases of poisoning; thirdly, it is often of the greatest importance for a medical man in a court of law to be able to state what are the symptoms and post-mortem appearances produced by a given poison, what diseases they simulate, and how far and in what they differ from the phenomena of these diseases. That part of the science of toxicology which treats of the recognition of poisons in the cadaver, or in food and drink, belongs to the domain of the chemist, and I have avoided it altogether. For a similar reason, in the sections on *materia medica*, the chemical relations of mineral substances have not been discussed at all.

## ABBREVIATIONS

- A. A.**—Archiv für Augenheilkunde.  
**A. A. P.**—Archiv für Anatomie und Physiologie.  
**A. C. J.**—American Chemical Journal.  
**A. D. S.**—Archiv für Dermatologie und Syphilis.  
**A. de P.**—Archives de Physiologie normale et pathologique.  
**A. E. P. P.**—Archiv für experimentelle Pathologie und Pharmacologie.  
**A. G. M.**—Archives générales de Médecine.  
**A. G. P.**—Archiv für die gesammte Physiologie des Menschen und der Thiere.  
**A. Hk.**—Archiv der Heilkunde.  
**A. I. B.**—Archives italiennes de Biologie.  
**A. I. M. N.**—Archivio italiano per le malattie nervose.  
**A. I. Past.**—Annales de l'Institut Pasteur.  
**A. I. P.**—Archives internationales de Pharmacodynamie.  
**A. J. M. S.**—American Journal of the Medical Sciences.  
**A. J. P.**—American Journal of Physiology.  
**A. K. C.**—Archiv für klinische Chirurgie.  
**Al. Z. Ps.**—Allgemeine Zeitschrift für Psychiatrie.  
**A. M. Ex.**—Archives de Médecine expérimentelle et d'Anatomie pathologique.  
**Amer. Med.**—American Medicine.  
**Am. Lan.**—American Lancet.  
**A. N.**—Alienist and Neurologist.  
**An. d'H.**—Annales d'Hygiène.  
**An. O.**—Annals of Ophthalmology.  
**Ann. O.**—Annales d'Oculistique.  
**A. Op.**—Archiv für Ophthalmologie.  
**A. of Op.**—Archives of Ophthalmology.  
**A. Ph.**—Archiv für Anatomie und Physiologie, physiologisches Abtheilung.  
**A. Pharm.**—Archives de Pharmacodynamie.  
**A. R.**—Aerztliche Rundschau.  
**A. S. Z.**—Aerztliche Sachverständigen-Zeitung.  
**Aus. M. Gaz.**—Australian Medical Gazette.  
**Aus. M. J.**—Australian Medical Journal.  
**A. V. K.**—Archiv für Verdauungskrankheiten.  
**A. Z.**—Apotheker-Zeitung.  
**B. A. M.**—Bulletin de l'Académie de Médecine de Paris.  
**B. A. R. B.**—Bulletin de l'Académie Royale de Médecine de Belge.  
**B. G. T.**—Bulletin général de Thérapeutique médicale et chirurgicale.  
**B. K. Ch.**—Beiträge zur klinischen Chirurgie.  
**B. K. W.**—Berliner klinische Wochenschrift.  
**B. M.**—Le Bulletin Médicale.  
**B. M. J.**—British Medical Journal.  
**B. M. S. C. P.**—Bulletin et Mémoires de la Société Clinique de Paris.  
**B. M. S. H.**—Bulletin Société Médicale des Hôpitaux des Paris.  
**B. M. S. J.**—Boston Medical and Surgical Journal.  
**B. P. A.**—Beiträge zur Pathologischen Anatomie und zur Allgemeinen Pathologie.  
**Cb. B.**—Centralblatt für Bacteriologie.  
**Cb. C.**—Centralblatt für Chirurgie.  
**Cb. I. M.**—Centralblatt für Innere Medicin.  
**Cb. N.**—Centralblatt für Nervenheilkunde.  
**Cb. P.**—Centralblatt für Physiologie.  
**C. B. S. A.**—Correspondenzblatt der Schweizerische Aerzte.  
**Chi. M. J.**—Chicago Medical Journal.  
**C. K. M.**—Centralblatt für klinische Medicin.  
**Cl. M.**—Clinica Moderna.  
**Cl. M. I.**—La Clinica Medica Italiana.  
**C. M. J. E.**—Chicago Medical Journal and Examiner.  
**C. M. R. V.**—Contributions to Medical Research. Vaughn. Ann Arbor. 1903.  
**C. M. W.**—Centralblatt für medicinischen Wissenschaften.  
**C. R. A. S.**—Comptes-rendus de l'Académie de Science, Paris.  
**C. R. S. B.**—Comptes-rendus de la Société de Biologie, Paris.  
**D. A. K. M.**—Deutsches Archiv für klinische Medicin.  
**D. C.**—Dermatologisches Centralblatt.  
**D. J. M. S.**—Dublin Journal of the Medical Sciences.

- D. Kl.**—Deutsche Klinik.  
**D. M. W.**—Deutsche medicinische Wochenschrift.  
**D. Z. Ch.**—Deutsche Zeitschrift für Chirurgie.  
**D. Z. N.**—Deutsche Zeitung für Nervenheilkunde.  
**Ed. M. J.**—Edinburgh Medical Journal.  
**E. M. N.**—L'Écho Médical du Nord.  
**Fort. M.**—Fortschritte der Medicin.  
**G. A. M. T.**—Giornale della Reale Accademia di Medicina di Torino.  
**G. H. M. C.**—Gazette Hebdomadaire de Médecine et de Chirurgie.  
**G. I. M. P.**—Gazzetta Internazionale de Medicina Practica.  
**G. K. H.**—Monatsberichte über die gesamtleistungen auf dem Gebiete der Krankheiten des Harn und Sexual-Apparates.  
**G. M. P.**—Gazette Médicale de Paris.  
**Gl. M. J.**—Glasgow Medical Journal.  
**Guy H. R.**—Guy's Hospital Reports.  
**Hk.**—Die Heilkunde.  
**H. S. Jb.**—Hoffmann und Schwalbe's Jahresberichte über die Fortschritte der Anatomie und Physiologie.  
**I. B. I. M.**—Internationale Beiträge zur Inneren Medicin.  
**In. Dis.**—Inaugural Dissertation.  
**J. A. M. A.**—Journal of the American Medical Association.  
**J. A. P.**—Journal of Anatomy and Physiology.  
**J. Chem. S.**—Journal of the Chemical Society of London.  
**J. de l'A. P.**—Journal de l'Anatomie et Physiologie.  
**J. de Th.**—Journal de Thérapeutique.  
**J. Ex. M.**—Journal of Experimental Medicine.  
**J. M. R.**—Journal of Medical Research.  
**J. N. M. D.**—Journal of Nervous and Mental Diseases.  
**J. P.**—Journal of Physiology.  
**J. Pr.**—Journal des Praticiens.  
**J. P. and B.**—Journal of Pathology and Bacteriology.  
**K. T. W.**—Klinisch-Therapeutische Wochenschrift.  
**L. L.**—London Lancet.  
**Lyon M.**—Lyon Médicale.  
**L. M. R.**—London Medical Recorder.  
**L. S.**—Lo Sperimentale.  
**M. A.**—Merck's Archives.  
**M. C. C.**—Medicinische-Chirurgisches Centralblatt.  
**M. C. Tr.**—Medico-Chirurgical Transactions.  
**Med. R.**—Medical Register.  
**M. H. H. B.**—Marine Hospital Hygienic Laboratory Bulletin.  
**M. M. W.**—Münchener medicinische Wochenschrift.  
**M. News.**—Medical News.  
**M. N. A. S.**—Memoirs of the National Academy of Science.  
**M. P. D.**—Monatshefte für praktische Dermatologie.  
**M. P. N.**—Monatsschrift Psychiatrie und Neurologie.  
**M. R.**—Merck's Report.  
**M. S. Rep.**—Medical and Surgical Reporter.  
**M. T. G.**—Medical Times and Gazette.  
**M. W.**—Medicinische Wochenschrift.  
**N. Ch.**—Neurologisches Centralblatt.  
**N. O. M. J.**—New Orleans Medical Journal.  
**N. Y. M. J.**—New York Medical Journal.  
**N. Y. M. R.**—New York Medical Record.  
**N. Y. M. T.**—New York Medical Times.  
**O. M. R.**—Ohio Medical Recorder.  
**O. R.**—Ophthalmic Record.  
**Pa. M. S. J.**—Pacific Medical and Surgical Journal.  
**Path Intern.**—Pathologie Interne.  
**Ph. Post.**—Pharmaceutical Post.  
**P. J. and Tr.**—Pharmaceutical Journal and Transactions.  
**P. M. C. P.**—Pester medizinisch Chirurgische Presse.  
**P. M. J.**—Philadelphia Medical Journal.  
**P. M. T.**—Philadelphia Medical Times.  
**P. P. S. L.**—Proceedings of the Physiological Society of London.  
**Pract.**—Practitioner.  
**Press. M. B.**—La Presse Médicale Belgique.  
**Pr. M. W.**—Prager medicinische Wochenschrift.  
**Prog. M.**—Le Progrès Médicale.  
**P. Tr. R. S. L.**—Philosophical Transactions of the Royal Society of London.  
**Q. J. P. M.**—Quarterly Journal of Psychological Medicine and Medical Jurisprudence.  
**R. C.**—Revue de Chirurgie.  
**R. M. S. R.**—Revue Médicale de la Suisse Romande.  
**R. Med.**—Revue de Médecine.  
**Rif. M.**—La Riforma Medica.  
**R. T.**—Revue de Thérapeutique.  
**Sb. G. W.**—Sitzungsberichte der königliche Gesellschaft der Wissenschaften.  
**S. Jb.**—Schmidt's Jahrbücher der in- und ausländischen gesammten Medicin.  
**S. M.**—La Semaine Médicale.  
**St. L. C. R.**—St. Louis Clinical Record.  
**St. L. M. S. J.**—St. Louis Medical and Surgical Journal.



- S. L. P. C. Y.**—Studies from the Laboratory of Physiological Chemistry of Yale University.
- St. P. M. W.**—St. Petersburger medicinische Wochenschrift.
- T. G.**—Therapeutic Gazette.
- Ther. Geg.**—Die Therapie der Gegenwart.
- Th. M.**—Therapeutische Monatshefte.
- T. M.**—Therapeutic Monthly.
- Tr. A. O. S.**—Transactions of the American Ophthalmological Society.
- Tr. I. C. C.**—Transactions of the International Congress of Charity, Corrections, and Philanthropy.
- Tr. P. C. M. S.**—Transactions of the Philadelphia County Medical Society.
- Tr. R. S. Ed.**—Transactions of the Society of Edinburgh.
- T. W.**—Therapeutische Wochenschrift.
- U. M. M.**—University Medical Magazine.
- U. N. M. T.**—Untersuchungen zur Naturlehre des Menschen und der Thiere. Moleschott.
- U. P. L. W.**—Untersuchungen aus den Physiologisches Laboratorium zu Würzburg.
- U. P. M. B.**—University of Pennsylvania Medical Bulletin.
- V. A. P. A.**—Virchow's Archiv für pathologische Anatomie und Physiologie.
- V. A. S.**—Verein der Aerzte in Steiermark.
- V. C. M.**—Verhandl. des Congresses für Innere Medizin.
- V. V. N. K. I. M.**—Verhandlungen des Vierten Nordischen Kongresses für Innere Medizin.
- W. A. W.**—Sitzungsberichte der kaiserlichen Akademie der Wissenschaften zu Wien. Math. Naturwiss. Kl.
- W. G. H.**—Wochenschrift für die gesammte Heilkunde.
- Wb. G. A. W.**—Wochenblatt der k. k. Gesellschaft der Aerzte in Wien.
- W. K. R.**—Wiener klinische Rundschau.
- W. K. W.**—Wiener klinische Wochenschrift.
- W. M. Bl.**—Wiener medicinische Blätter.
- W. M. P.**—Wiener medicinische Presse.
- Z. B.**—Zeitschrift für Biologie.
- Z. C. P. P.**—Zeitschrift (Beiträge) zur Chemischen Physiologie und Pathologie.
- Z. F. H. I.**—Zeitschrift für Hygiene und Infektionskrankheiten.
- Z. K. M.**—Zeitschrift für klinische Medizin.
- Z. Mb.**—Zeitschrift für Medicinalbeamte.
- Z. P. C.**—Zeitschrift für physiologische Chemie.



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# THERAPEUTICS:

## ITS PRINCIPLES AND PRACTICE

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### DRUGS:

A SKETCH OF THEIR NATURAL HISTORY AND PHARMACEUTICAL PREPARATIONS, WITH AN EXHAUSTIVE STUDY OF THEIR PHYSIOLOGICAL, THERAPEUTICAL, AND TOXICOLOGICAL ACTIONS.

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### PRELIMINARY CONSIDERATIONS.

THERAPEUTICS is the science of the treatment of disease, including the use not only of chemical agencies (drugs), but also of various physical agencies, and the regulation of the mode of living. The science which treats of drugs is called PHARMACOLOGY. Pharmacology includes MATERIA MEDICA, the study of the physical properties of substances used as medicines; PHARMACY, the science of preparing and combining drugs; and PHARMACODYNAMICS, or the study of the effect of drugs upon the healthy animal organism (physiological action).

In every civilized country there is some recognized official list of drugs and their preparations, known as the *Pharmacopœia*. Until recently the United States Pharmacopœia was the standard by courtesy, rather than legal enactment, but adherence to its rules is now required by the Federal government as well as by most of the States.

Drugs are derived from the animal, mineral, and vegetable kingdoms; the greater number of them, however, are of vegetable origin. Vegetable drugs as a rule contain some definite chemical substance to which they owe their remedial properties, and which is, therefore, known as the active principle.

A number of these active principles belong to the class of substances known as alkaloids. An *alkaloid* may be defined as a substance of vegetable origin which is capable of playing the part of an

alkali in so far that it forms salts with the acids. As a rule alkaloids themselves are not freely soluble in water, but the salts which they form are very frequently so; therefore, with one or two exceptions the alkaloids are usually employed in the form of some salt. Examples: Morphine, Strychnine, etc.

A *glucoside* is a proximate principle of vegetable origin which can be broken up by mineral acids into a sugar and another radical. Examples: Strophanthin, Salicin, etc.

*Resins* are complex bodies uncrystallizable and usually insoluble in water, but freely soluble in alcohol, ether and chloroform. Many of them have acid properties. Allied to the resins are the so-called *oleoresins*, which are really mixtures of a resin with a volatile oil.

The *volatile oils* represent the active principles especially of many aromatic plants. They have a strong odor, are very slightly soluble in water, but usually soluble in alcohol and ether. They differ from the fixed oils in their greater aroma, but especially in the fact that when evaporated they leave behind no residue, and that they are not saponified by the alkalies. Examples: Oil of Wintergreen, Oil of Peppermint, etc.

Many principles of indefinite character have been grouped together under the head of *neutral principles*. These are usually of bitter taste but differ from alkaloids in that they do not form salts with the acids. Various *organic acids* may also be the active principles of drugs.

Remedial agents of organic origin usually require more or less pharmaceutical manipulation before they are suited for medical uses. The preparations which are made from drugs are commonly known as *galenicals*, from Galen, the famous Roman physician who lived in the second century.

The most important of the **official preparations** are:

**DECOCTIONS** (*Decocta*) are made by boiling crude drugs for a greater or less time in water. It is evident that this method of preparing is ineligible when the active principle is volatile or is easily decomposed by heat, or when the drug contains much starch, whose extraction would make the preparation very thick and predispose it to rapid decomposition. The method is especially adapted to hard, woody substances, and to those containing much albumin, which is coagulated by the boiling water and left in the original drug.

**INFUSIONS** (*Infusa*) are made with water, either cold or hot, without boiling. They are prepared by maceration or by displacement.

**SOLUTIONS** (*Liquores*) are preparations in which an active, *non-volatile* principle is dissolved in water.

**WATERS** (*Aquæ*) are solutions of *volatile* principles in water.

**MIXTURES** (*Misturæ*) are preparations in which one or more medicinal substances are held in suspension in water. Of such nature are *emulsions* (*Emulsa*), in which some oily material is suspended by a *gummy* or an *albuminous* body.

**SYRUPS** (*Syrupi*) are sugary liquids, the menstruum or basis of which is water, with, in some cases, vinegar or alcohol.



FLUIDEXTRACTS (*Fluidextracta*) are solutions of vegetable drugs in alcohol, so made that one minim represents one grain of the drug.

TINCTURES (*Tincturæ*) are alcoholic solutions prepared by maceration or displacement from the crude drug, or by dissolving *non-volatile* principles. They are of varying strengths from 5 to 50 per cent.; the poisonous tinctures are nearly all 10 per cent. preparations.

SPIRITS (*Spiritus*) are alcoholic solutions of volatile principles, made by direct solution or by distillation from the crude drugs.

WINES (*Vina*) are preparations whose menstruum is wine.

VINEGARS (*Aceta*) are preparations in which vinegar or dilute acetic acid is used as the menstruum.

GLYCERITES (*Glycerita*) are preparations in which glycerin is the solvent.

OLEATES (*Oleata*) are solutions of definite principles in oleic acid.

SOLID EXTRACTS (*Extracta*) are of two kinds; one being prepared by the evaporation of the fresh juice, the other being made in various ways from the crude drug. They are of a consistency suitable for making pills.

CONFECTIONS (*Confectiones*) are medicinal substances beaten up with sugar into a pasty mass.

TROCHES (*Trochisci*), or *lozenges*, are gummy pellets or disks, so made as to dissolve slowly in the mouth.

SUPPOSITORIES (*Suppositoria*) are conical bodies, prepared for introduction into the rectum, where they melt with the heat of the body. Their basis is generally cacao butter.

OINTMENTS and CERATES (*Unguenta* and *Cerata*) are solid, fatty preparations for external use. The cerates containing wax (*cera*) are the firmer of the two.

PLASTERS (*Emplastra*) are solid substances spread by the aid of heat upon muslin, skin, or other similar material, and of such nature as to be adhesive at the temperature of the body.

LINIMENTS (*Linimenta*) are liquid preparations, for external use.

The names PILLS (*Pilulæ*) and POWDERS (*Pulveres*) sufficiently indicate the character of the preparations.

The effects of medicine are commonly divided into the *direct* and *indirect*. An example will probably show the difference between these in the briefest and most forcible manner. Thus, the direct effect of a diuretic is increased urination; the indirect effect may be removal of serous effusion in some part of the body which is brought about not by the medicine itself, but by the changes it induces; the increased excretion causing a diminution of the amount of the fluid in the blood-vessels, which in turn leads to absorption. The term *local action* indicates the effects of drugs upon that part of the body with which they first come in contact, as the stomach; by *general action* is understood their effects on distant parts of the body to which they are carried by the blood after being absorbed.

The term or expression "*indication*" for a given remedy, being in constant use, ought to be clearly understood; by it is meant the

pointings of nature, or, in other words, the evident needs of the system. Thus, hard feces collected in the colon are an indication for a purgative of such character as will produce watery secretions to soften them. Relaxation in a part indicates a remedy that will awaken into new life the natural contractility of the part—i.e., an astringent.

**Methods of Administering Drugs.**—To exercise a general action drugs must be absorbed into the blood, and thus find access to the part upon which they act. It is necessary, therefore, for them to be so placed that they can be taken into the blood-vessels.

There are six paths of entrance for medicines into the circulation,—the stomach, the cellular tissue, the rectum, the skin, the lungs and by intravenous injection. By far the most frequently employed of these is the stomach. It is evident that, in order to pass rapidly and readily into the absorbents, medicines must be in solution. When administered by the stomach, however, it is equally plain that solubility in an ordinary menstruum, such as water, is not a *sine qua non*, since the varying acidities, alkalinities, and organic contents of the alimentary juices give to them a solvent power far above that of less complex and varying fluids. Thus, a medicine insoluble in water may be dissolved by the acids of the gastric juice, while another drug may owe its activity to its solution by the alkalies or by the fatty matters of the intestinal fluids.

The dissolving power of the rectal fluids is very slight: hence, in order to act efficiently, medicines when given by the rectum must be in solution or be readily soluble. Absorption, moreover, does not occur so rapidly from the rectum as from the upper bowel, and a longer time is therefore needed to impress the system in this way.

Medicines which are thrown into the subcutaneous tissue are said to be administered hypodermically. The syringe employed is provided with a sharp needle, which must be kept scrupulously clean and free from rust. The medicine must be in perfect solution and not too irritating. The advantages of this method of exhibition are promptness and certainty of action. If twenty minutes be required for the absorption of a certain medicine from the stomach, forty minutes will be usually necessary when it is exhibited by the rectum and five minutes when it is thrown into the subcutaneous tissue. The objections to the hypodermic method are, first, the danger of producing local inflammation and abscesses; second, the possibility of throwing the whole mass directly into a vein and having it swept in concentrated form into the heart or nerve-centres. We have seen the injection of one-sixth of a grain of morphine followed inside of a minute by complete unconsciousness, collapse, arrest of respiration, dropping of the jaw, and apparent death. The danger of such a mischance can be greatly lessened by withdrawing the point of the needle an eighth of an inch, after it has been plunged into the tissue. The local irritation occasioned by hypodermic injections has not only very frequently produced abscesses, but in not a few cases has caused

fatal tetanus. Excessive irritation can be largely prevented by certain precautions, but there are many medicinal substances whose hypodermic employment might be advantageous were they not too irritant for such use. In all cases solution must be complete, and if the medicinal substance be of such nature that it is liable to be precipitated by alkalies, an excess of acid should be present in the water to prevent precipitation by the juices of the cellular tissue. An irritant which is rapidly taken up from the part may produce at first smarting and pain without creating any permanent irritation, but a small solid particle lying in the cellular tissue is almost sure to cause inflammation and abscess. All hypodermic injections should, therefore, be filtered before being used. It is of the utmost importance, even when a non-irritating substance is employed, that the injection should be absolutely aseptic. No solution which has undergone any decomposition or contains any growth should be used. Ordinarily the solution should be freshly made with boiled water. When hypodermic solutions are intended to be kept, they should contain three per cent. of phenol with a drop or two of glycerin to every fifteen minims, which is the maximum amount that should be injected at one time. A considerable proportion of glycerin will throw out of solution most of the alkaloids, but when solution of the medicinal substance is distinctly favored by glycerin, as is the case with extracts, three or four minims of the glycerin should be added to the hypodermic solution. If the injection be thrown directly under the skin, it may, by raising and tearing the skin from its attachment, so interfere with the supply of blood as to cause local irritation. Irritant substances should, therefore, always be thrown deeply into the tissues, where they may diffuse themselves.

The skin can be used successfully as a mode of introducing drugs only if the medicament is volatilizable or else is in fatty solution, as in certain ointments. Formerly, medicines were sometimes exhibited by placing them on blistered surfaces, beneath the raised cuticle; at present this endermic method is very rarely employed.

In order for a medicine to be absorbed through the lungs it must be vaporizable at the body temperature, and not too irritant to be inhaled.

The intravenous injection, on account of the dangers and the elaborate technique required, is rarely resorted to except in extreme cases.

For *local* purposes medicines are applied to various parts,—to the skin, ear, nares, fauces, stomach, larynx, lungs, rectum, vagina, urethra, etc. For the last three, liquid preparations known as *injections*, or solid ones known as *suppositories*, or, in case of the urethra, as *bougies*, or sometimes as *urethral suppositories*, are employed.

For the purpose of making local applications to the respiratory organs, *atomization* is very commonly practised. Many forms of apparatus are in use, but the principle in all of them is the same. A rapid current of air, or of steam, is forcibly ejected from a hori-



zontal pipe, through a capillary orifice, directly across a similar opening in a vertical tube. The rush of the vapor over this second orifice forms a vacuum; the fluid into which the base of the vertical tube is set, rushing up to fill this, is sucked or drawn out through the orifice, and as it emerges is broken into a fine spray, and is carried along by the current of air or steam into a mouthpiece, at which sits the patient. It cannot be gainsaid that in this way we are able to carry medicinal substances not merely into the larynx, but into the lungs themselves. Volatile medicines vaporized by heat are also sometimes employed in the treatment of lung affections.

† There are various classes of agencies which so modify the action of drugs as to necessitate their consideration. Such are disease, climate, habit, temperament, idiosyncrasies, sex, age, time of administration, and emotions.

*Disease* often fortifies the system against the action of remedies, so that the dose has to be greatly increased to obtain perceptible effects. Thus, pain or delirium tremens will interfere greatly with the production of narcotism by opium. Disease may altogether prevent the action of a remedy. In all these cases two rules should never be lost sight of: first, never give the medicine in such doses as would in health cause death; second, always be sure, before giving large amounts, that the remedy will not make matters worse (as a drastic purgative in intussusception).

*Climate*, by producing physical habits or tendencies in the patient, often greatly influences the proper selection and dose of remedies. It is only necessary to allude to the great consumption of quinine in malarial regions as an example.

*Habit—including mode of life*—seems to alter, as it were, the very constitution of man. Not only does it give type to disease, by producing habitual plethora, or its opposite, but it also fortifies against the action of single remedies, or whole classes of them. Thus, in the opium-eater, a dose sufficiently large to kill an ordinary man serves only to gratify the cravings of appetite. Again, a man accustomed to one narcotic, as alcohol or opium, loses, to a greater or less degree, his susceptibility to all narcotic influence; and the patient whose bowels require daily to be moved by a cathartic finds that he reacts more and more slowly to medicines of that class. Again, a nervous system blunted by exposure and toil in the open air is far less susceptible to the action of remedies, and requires larger doses to influence it, than does the delicate organization of a woman weakened by indolence and luxury.

*Temperaments* are peculiarities of organization characterizing classes of individuals: *idiosyncrasies*, peculiarities belonging to single individuals. This is scarcely the place to discuss the subject of temperaments, but it is allowable to state that while the *phlegmatic* person is no more easily moved by medicinal than by other agencies, the *nervous* individual answers as quickly to the one as to the other. Idiosyncrasies seem at present to be beyond law. They are often



very remarkable, and a knowledge of them is most important for the practitioner. Thus, a relative of the authors' is thrown into the most alarming fainting-fits by eating even so much butter as would be ordinarily used as a dressing for vegetables at dinner. Some persons are poisoned by the slightest touch of turpentine, others are frightfully salivated by a mere particle of a mercurial. These idiosyncrasies are numerous, cannot be foreseen, and are often very important: hence the necessity, in prescribing for an unfamiliar patient, of always asking as to his or her peculiarities.

*Sex* modifies all diseases connected with the organs or the process of generation, but it also does more. Woman is more impressible, less robust, with less power of resisting external agencies, than is man; consequently, the dose for her should, as a rule, be less than that for him. It is needless to remark here at length on the necessity for abstinence from strongly perturbing remedies during pregnancy or at menstrual periods.

*Age*, of course, modifies materially the dose. The rule of Young, the one which is the most practical and generally useful, is to add twelve to the age and divide the age by the result. Thus, a child one year old would require one-thirteenth, one three years old three-fifteenths, of the amount necessary for an adult.\*

Purgatives should usually be given to children in larger, narcotics in much smaller, doses than are called for by Young's rule.

*Time of Administration.*—Absorption takes place most rapidly in an empty stomach, and consequently, when rapidity of action is desired, the medicine should be given under such circumstances. Thus, a purgative acts soonest when given before breakfast. Substances which are irritating to the stomach should always be administered, not only properly diluted, but also when the viscus is filled by a mass of food, which may serve still further to lessen their concentration. Hence such remedies as iodine and arsenic are preferably exhibited after meals. On the other hand, whenever a remedy is especially intended to act on the mucous membrane of the stomach, it should be given when the viscus is empty. Again, some drugs, such as iron, are best dissolved by the acid gastric juice, and it is a matter of some importance to place them in the stomach after eating, when the process of digestion is most vigorous.

*Mental Emotion.*—Space is wanting to discuss at any length the influence of the imagination upon the action of remedies, and the reader is referred to the delightful book of Tuke for illustrations. Suffice it to state that a positive announcement that a remedy will have a certain effect has often a most remarkable influence in pro-

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\* Clarke's rule (*Boston Med. and Surg. Journ.*, 1872) is based upon relative weight.

"Assuming the average weight of an adult to be one hundred and fifty pounds, for whom an appropriate dose is 1, or one drachm, the dose of most medicines must be increased or diminished in the proportion of the weight of the patient to that number of pounds. This proportion is represented by a fraction whose numerator is the patient's weight and whose denominator is 150. If a child at birth weighs six pounds, the appropriate dose for it would be  $\frac{1}{25}$ , or  $\frac{1}{25}$ ; if it weighs ten pounds,  $\frac{2}{15}$ , or  $\frac{2}{15}$ . A child two years old, weighing twenty pounds, would require  $\frac{2}{7.5}$ , or about  $\frac{1}{4}$  of an adult dose; or, more precisely,  $\frac{2}{7.5}$ . A person whose weight is two hundred pounds should have  $\frac{4}{3}$ , or  $1\frac{1}{3}$  of an average adult dose."

ducing that effect, especially on persons of nervous organization and of not too great culture to have faith. We have given a hypodermic injection of one-fourth grain of morphine to a man, inducing a degree of hypnotism, and the next day, doubling the size of the injection but withdrawing all morphine, have caused a much more intense effect.

**On the Art of Prescribing Medicines.**—In the practical use of remedies, very much depends upon the methods of their combination, and, so far as concerns the reputation of the physician, no little importance is to be attached to the mere prescription-writing. The recipes of the master are very widely seen, and he who is incorrect in the grammar or spelling of his English or Latin, or departs without reason from the traditional forms, lays himself open to ridicule, than which nothing is more damaging. A crooked, bad chirography is the traditional mark of literary fame; but absolute plainness should be a *sine qua non* in the writer of prescriptions. This should also apply to abbreviations: these should be of such a character as not only to be readily made out, but also to be so evident as to afford no shelter to the apothecary whose carelessness may lead to serious error. In the case of alkaloids and other powerful remedies, the chief name at least should be written in full. In writing the prescription, all the ingredients should first be put down, then the number of doses should be decided upon, and the individual amounts of each substance marked *seriatim*. It is a very good custom always to place first upon the list the strongest of the drugs employed.

The art of combining remedies is not a difficult one; but in practice certain principles should not be lost sight of. Chief of these are, to prescribe as few remedies as possible, and to use no powerful drug without a very distinct idea of what it is intended to do. Whenever it is desired to give a powerful remedy in increasing doses until its physiological effect is produced, it should always be given by itself. Thus, it may be necessary to give arsenic so as to impress the system, at the same time that iron is indicated; but the two remedies should be given separately, so that the dose of either can be increased or diminished independently of the other.

The principles of combination, formulated below, were long ago enunciated by Paris, but are to-day as imperative as ever. Medicines are combined,—

*First.*—To augment, correct, or modify the action of a medicine. Thus, purgatives act much more kindly when a number of them are united together. The chief reason of this probably is, that as different remedies affect different portions of the gut, the whole intestine is best reached by a union of the diverse substances. It may take an intense irritation of the mucous membrane to purge as actively as does a mild irritation of both the mucous membrane and the muscular coat.

There are powerful medicines which act similarly upon some parts of the organism, but dissimilarly upon other parts. By combining such remedies powerful effects can be obtained at the points where

the two lines of action cross each other, without influencing to a great extent other portions of the system. Thus, chloral produces sleep by its action upon the brain, and also has a distinct influence upon the heart, but none upon the intestinal tract. Morphine acts upon the brain, and does not influence the heart, but has a powerful effect upon the intestinal tract. By combining chloral and morphine we get an overwhelming conjoined influence upon the brain in producing sleep with the least possible disturbance of the heart and of the intestinal tract.

*Secondly.*—To obtain the joint action of two or more diverse remedies. Thus, in a cough mixture, morphine may be included to quiet the cough, while ipecacuanha and squill (in accordance with the first principle) are added to affect the mucous membrane. The application of this principle requires caution, or the practitioner will be led into that chief abomination, polypharmacy. It is worse than futile to attempt to prescribe for every symptom. It is the underlying cause of the disorder or the understratum of bodily condition which must be sought out and prescribed for simply.

*Thirdly.*—To obtain a special combination which is really a new remedy, or which experience has shown acts almost as a new remedy. Thus, when to potassium iodide in solution corrosive sublimate is added, a new chemical compound is formed, which experience has shown to be of great value in syphilitic diseases. In the famous Dover's powder (*Pulvis Ipecacuanhæ et Opii*) no chemical change occurs, but the ordinary action of opium upon the skin is so enhanced that the combination may be looked upon almost as a new remedy.

*Fourthly.*—To afford a suitable form. Thus, acacia is added to make an emulsion, or confection of rose to make a pill. In the choice of excipients, care should be exercised to select a substance free from medical properties, having no chemical incompatibility with the medicinal agent, and of suitable physical character. When writing a prescription, the utmost care should be taken to use such excipients that the combination shall not only be attractive to the eye, but also as slightly repulsive to the palate as may be. Whenever possible, the pill form should be employed with bitter or disagreeable medicines. In regard to mixtures, flavoring oils should be freely used, and the power of glycerin to conceal the disagreeable taste of many substances should be remembered. Whenever practicable, nauseous medicines should be given in capsules. These occur in two forms. *Hard* capsules are prepared to be filled extemporaneously. They can be made large enough to hold ten grains, although this size cannot be easily swallowed by every person without a little training. The soft, flexible capsules are filled by the manufacturing chemists. They can be readily swallowed by most persons up to the size of one drachm. Not only may solid preparations be given in capsules, but also essential oils, volatile liquids, fixed oils, and fluidextracts; indeed, almost any liquid the dose of which is not too large.



**INCOMPATIBILITIES.**—In combining remedies, the subject of incompatibilities must never be lost sight of. The kinds of incompatibilities are three in number,—physiological, pharmaceutical and chemical. The first of these it would require large space to discuss fully, and any one familiar with the text of the book, if possessed of the slightest reasoning powers, can readily make all necessary deductions.

Pharmaceutical incompatibilities are mostly dependent on the different solvent powers of water and alcohol. Speaking generally vegetable substances are more readily soluble in alcohol than in water. For this reason the alcoholic tinctures contain various resinous matters which are insoluble in water, and the mixture of such a tincture with an aqueous menstruum frequently causes a precipitation which makes an unsightly mixture or may even interfere with its efficacy. In this connection attention may be called to the precipitation of acacia by alcohol; therefore emulsions should always be made with a watery menstruum.

The inorganic drugs are more generally soluble in water than in alcohol. For accurate data concerning the solubility of official chemicals the reader is referred to the United States Pharmacopœia; but the most important relations are covered by the following rules: All of the official salts of potassium, except the bitartrate, are soluble in water; all the official salts of sodium and of ammonium are soluble in water; all the salts of mercury except the bichloride are insoluble; the salts of the other bases vary in their solubility too much to allow a brief summarization. All of the official salts of the following acids are soluble: Hydrobromic, hydrochloric, hydriodic, acetic, citric, benzoic and salicylic. Basic alkaloids are, as a rule, almost insoluble in water, their salts are usually easily dissolved by water but less readily by alcohol.

In many works on *materia medica* long lists of chemical incompatibilities are given in the accounts of individual drugs. These lists have seemed to us useless, as we have never met with a student who could commit and retain them. Moreover, they contain so much matter of no practical use that the valuable portion is hidden from sight. A certain amount of chemical knowledge is essential to the student, and is not to be taught in a book like the present. He who would ignorantly combine sulphuric acid and the carbonates, needs to restudy his chemical text-book. All that we shall do here is to point out certain principles and a few reactions. The following rules may serve as a guide.

When two salts can, by any change of their radicals, form an insoluble compound such change will take place and precipitation occur; soluble salts which are not capable of forming an insoluble compound never precipitate and rarely undergo decomposition when they meet in solution.

*Mineral acids* decompose salts of the vegetable (carbonic, acetic, etc.) acids and form ethers with alcohol. They also decompose the glucosides.



Salts of the *alkaloids* are precipitated from aqueous solution by the alkalies including carbonates and borates, by the iodides,\* corrosive sublimate and tannic acid. *Antipyrine* is incompatible with all the alkaloidal precipitants and also with spirit of nitrous ether, with tincture of ferric chloride, and with calomel; it is liquefied by hydrated chloral, by salol and by various other members of the aromatic series.

*Tannic acid* is incompatible with the alkaloids, glucosides, gelatin, albuminous bodies and most of the soluble metallic salts.

*Silver nitrate* and *corrosive sublimate* are each incompatible with almost every drug in the Pharmacopœia, as are also the acetate and subacetate of lead.

Preparations containing *iron* are incompatible with salicylic acid and its salts. With nearly all the vegetable galenicals they form a black precipitate due to the fact that practically all vegetable products contain tannic acid—from this latter group may be excepted quassia and calumba. The salts of iron are also precipitated by alkalies.

The following preparations contain free acid and should not be prescribed with alkaline carbonates: Fluidextracts of conium, ergot, lobelia, nux vomica, sanguinaria and squill; the syrups of squill, ipecac, hypophosphites and orange; the solutions of ferric chloride, of hydrogen dioxide and of iron and ammonium acetate, and frequently the spirit of nitrous ether. The following are alkaline in reaction and should not be combined with acids: Aromatic fluid-extract of cascara sagrada, fluidextracts of licorice, of senega, and of taraxacum, the solution of potassium arsenite and the syrup of rhubarb.

**Classification.**—While it is impossible to devise any arrangement of drugs which is perfectly satisfactory in all respects, the following schema, which follows the principle of all systematic arrangements in biological science, is, we believe, of great service to the student in enabling him to associate together drugs having similar effects.

**DIVISION I.**—SYSTEMIC REMEDIES, substances which act on the solid or fluid tissues of the body.

**DIVISION II.**—EXTRANEOUS REMEDIES, substances which are employed to act on secretions, excretions, or other liquid or solid bodies which are not human tissues.

## SYSTEMIC REMEDIES.

**CLASS I.**—GENERAL REMEDIES, drugs which affect the tissues of the body generally or such organized systems as reach all portions of the body.

**ORDER I.**—*Nervines*, drugs which affect the nervous system.

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\* Death has resulted from a prescription containing strychnine and potassium iodide, all the alkaloid being taken at the last dose.

ORDER II.—*Cardiants*, drugs which affect the circulation.

ORDER III.—*Nutriants*, drugs which affect the nutritive processes of the body.

### NERVINES.

A. Medicines which act on the cerebrum.

B. Medicines which act on the lower or neuro-muscular apparatus.

#### A.

FAMILY I.—*Calmatives*, feeble cerebral stimulants which are employed for the relief of minor spasms and other nervous symptoms, the result of insufficient nerve-power.

FAMILY II.—*Anesthetics*, drugs which are used for the production of anesthesia.

FAMILY III.—*Somnifacients*, drugs which when in sufficient doses produce deep sleep without delirium.

FAMILY IV.—*Delirifacients*, drugs which when in sufficient doses produce delirium, followed by stupor.

#### B.

FAMILY V.—*Excito-motors*, drugs which produce violent tetanic spasms.

FAMILY VI.—*Depresso-motors*, drugs which cause paralysis.

### CARDIANTS.

FAMILY I.—*Cardiac Stimulants*, drugs which increase the activity of the heart.

FAMILY II.—*Cardiac Depressants*, drugs which lessen the heart action.

### NUTRIANTS.

FAMILY I.—*Astringents*, drugs which call into exercise the vital function of contractility.

FAMILY II.—*Tonics*, drugs which so influence nutrition as to increase the reconstruction or upbuilding of the tissue or tissues concerned.

FAMILY III.—*Alteratives*, drugs which so modify nutrition as to overcome certain chronic pathological processes.

FAMILY IV.—*Antiperiodics*, drugs which are used to overcome the effects of malarial poisoning.

FAMILY V.—*Antipyretics*, drugs which so modify nutrition as to overcome febrile movements.

CLASS II.—LOCAL REMEDIES, drugs which affect one organ or apparatus more or less isolated from the remainder of the body.

FAMILY	I.— <i>Stomachics</i> .*	FAMILY	VIII.— <i>Oxytotics</i> .
"	II.— <i>Emetics</i> .	"	IX.— <i>Irritants</i> .
"	III.— <i>Cathartics</i> .	"	X.— <i>Escharotics</i> .
"	IV.— <i>Diuretics</i> .	"	XI.— <i>Demulcents</i> .
"	V.— <i>Diaphoretics</i> .	"	XII.— <i>Emollients</i> .
"	VI.— <i>Expectorants</i> .	"	XIII.— <i>Protectives</i> .
"	VII.— <i>Emmenagogues</i> .		

## EXTRANEOUS REMEDIES.

FAMILY	I.— <i>Antacids</i> .	FAMILY	IV.— <i>Absorbents</i> .
"	II.— <i>Anthelmintic</i>	"	V.— <i>Disinfectants</i> .
"	III.— <i>Digestants</i> .		

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\* The definitions are not given in these families, as they are old and well known and their names show the reader to what organs each applies. It should be stated, however, that the family *stomachics* contains drugs which are used simply as stimulants to the gastro-intestinal tract, including, therefore, *Simple Bitters*, so called, and *Aromatics*.

## DIVISION I.—SYSTEMIC REMEDIES.

### CLASS I.—GENERAL REMEDIES.

#### ORDER I.—NERVINES.

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#### FAMILY I.—CALMATIVES.\*

IN certain conditions of the nervous system—conditions associated with weakness rather than with simple depression—the nerve-centres appear to be more susceptible than is normal to external impressions, as well as to those impulses which originate in the cerebral centres themselves and are connected with the emotions. As a result of this state arise symptoms ranging in their intensity from the simple state of unrest known as *nervousness* to the wildest convulsion of *hysteria*. It is in this class of affections that the so-called “antispasmodics” are useful. The drugs included in this group are nearly all possessed of only slight physiological power but of strong flavor, and it is not improbable that a large part of the benefit following their use is due to a psychical effect. As the diseases in which they are employed are associated with weakness it is believed, by some, that they are mildly stimulant to the central nervous system.

#### MUSK.

A highly odorous, unctuous substance, obtained from the glands situated just in front of the preputial orifice of the *Moschus moschiferus*, or musk-deer of Thibet. It is of brownish color with a very strong persistent odor and a bitterish taste. It is partly soluble both in alcohol and water, but not completely so in either menstruum. On account of its extraordinary high price it is very largely adulterated with various materials. The difficulty of obtaining pure musk and its expensiveness almost entirely precludes its use as a practical remedy.

#### Official Preparations:

Moschus.....	10 to 15 grains (0.6-1.0 Gm.).
Tinctura Moschi (5 per cent.).....	1 to 2 fluidrachms (4-8 C.c.).

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\* The term *Antispasmodics*, which was formerly applied to this group of drugs, has been such a fruitful source of confusion to the student, suggesting a relation to the motor depressants, that it has been thought wise to drop it as meaningless.



**Physiological Action.**—Musk appears to act upon the nervous system simply as a mild stimulant and antispasmodic. Jörg and Sundelin have experimented with it upon healthy men with somewhat contradictory results. According to the first-named observer, twenty grains of it induce exhilaration without lassitude, but, according to the latter authority, may cause giddiness, drowsiness, and lassitude. Both observers noted a slight increase in the frequency of the pulse.

**Therapeutics.**—Musk is at present very little used, but it is strongly recommended by some of the older writers in various spasmodic affections, especially in *hysterical convulsions*. In *hiccough* it has been considered a specific. In our experience, in the crisis of low fevers when the symptoms of nervous exhaustion are extreme and threaten death, musk is a very valuable remedy. Thus, in advanced *typhoid fever* a condition sometimes develops in which the pulse is exceedingly feeble, and the temperature has a tendency to rise to a great height, but yields almost immediately to the use of cold, only, however, to remount as soon as the cold is withdrawn. We have seen musk at such time control the temperature, steady the pulse, and apparently save life. In other cases of advanced fevers the powers of the system entirely give out, and the patient passes into a condition of collapse, with subnormal temperature, and mayhap coma-vigil: this state we have also seen relieved by musk. Originally recommended by Trousseau in the *ataxic pneumonia* of drunkards, musk may be a useful remedy in any forms of *adynamic pneumonia* when there is wild or muttering delirium. From ten to fifteen grains of musk (the best attainable) should be given at a dose, preferably by rectal injection, suspended in mucilage. The effect of the single dose lasts about six hours.

### VALERIAN.

The rhizome and roots of the *Valeriana officinalis*. This European plant is an herbaceous perennial growing to the height of from two to four feet, with pinnately compound leaves, and small pinkish flowers in compound cymes.

The official portion consists of a short, yellowish rhizome with numerous fibrous roots. It has a strong, disagreeable odor and a bitter camphoraceous taste. Valerian depends for its activity upon a volatile oil and the *valeric acid* which it contains.

#### Official Preparations :

Fluidextractum Valerianæ.....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Tinctura Valerianæ (20 per cent.).....	1 to 3 fluidrachms (4-10 C.c.).
Tinctura Valerianæ Ammoniata (20 per cent.)	1 to 3 fluidrachms (4-10 C.c.).

**Physiological Properties.**—The physiological action of valerian is very feeble. The extraordinary excitement which it produces in cats is probably due to a suggestive odor rather than to any direct influence. Large doses of valeric acid cause in rabbits some accelera-

tion of the pulse and respiration, followed by lessened frequency of these functions and general lassitude. Enormous doses may produce a fatal gastro-enteritis. According to Butte, the extract of valerian has a pronounced effect in checking the destruction of glucose in the blood.

Upon man, very large doses are said to produce a feeling of warmth in the stomach and quickening of the pulse, followed by nausea, vomiting, and colicky pains.

**Therapeutics.**—Valerian is useful in the state of unrest familiarly known as *nervousness*, and is much used in the minor disturbances of *hysteria*. It has been employed, though with little advantage, in *mania a potu* and *adynamic delirium* as an adjuvant to more powerful drugs.

AMMONIUM VALERATE or *Ammonium valerianate*, a white salt in quadrangular plates, effloresces in a dry and deliquesces in a moist atmosphere, has an odor resembling valerian and a sharp, sweetish taste, and is very soluble in water and in alcohol. According to W. E. Parke, it produces in the frog convulsions followed by general paralysis, both the convulsions and the palsy being of spinal origin, and also is capable by local contact of killing any of the higher nerve-tissues. These effects are probably due to the ammonia, and throw no light upon the therapeutic action of the drug, which is about equivalent to valerian, but sometimes has especial usefulness in *nervous headache*.

Ammonii Valeras.....10 grains (0.6 Gm.).

### ASAFETIDA.

An exudation obtained by incising the living root of the *Ferula foetida*, an umbelliferous plant of Afghanistan. It occurs mostly in irregular opaque masses of a dull yellowish or pinkish brown, white when freshly broken, of a bitter acrid taste and a strong garlicky odor. It is partly soluble in alcohol, although insoluble in water and when triturated with the latter yields a milky emulsion. Asafetida is composed chiefly of gum and resin, but its properties are in great part due to the volatile oil, of which it contains from three to nine per cent.

#### Official Preparations :

Pilule Asafœtidæ (each 3 grains).....2 to 4 pills.  
Tinctura Asafœtidæ (20 per cent.).....½ to 1 fluidrachm (2–4 C.c.).  
Emulsum Asafœtidæ (4 per cent.).....4 to 8 fluidrachms (15–30 C.c.).

**Physiological Action.**—When taken into the stomach, asafetida acts as a local stimulant and carminative, and on this account is in some parts of the East used as a condiment. The oil is without doubt absorbed. The evidence as to its action upon healthy men is both scanty and contradictory. Thus, while M. Pidoux took half an ounce

in a single dose without perceptible effects other than to render his secretions horribly offensive for two days, Jörg and his disciples found that in twenty-grain doses it produced gastric uneasiness and pain with alvine dejections, increased the pulse-frequency and animal warmth, quickened the respiration, and caused headache, giddiness, and erotic excitement.

**Therapeutics.**—Asafetida is the most efficient of the antispasmodics, and may often advantageously be substituted for valerian in *functional spasm*, in *hysteria*, and in *nervousness*. It differs from valerian in having a much more decided action upon the mucous membranes. It is an excellent *carminative*, and is constantly used as an enema for the relief of *tympanites*. It is valuable in *dyspepsia*, with flatulent colic and costiveness, of the aged or hysterical. As a *stimulating expectorant* and *antispasmodic*, it is useful in *whooping-cough* and in *chronic bronchial catarrh*, especially in old people with an asthmatic tendency. In *infantile convulsions*, in *infantile colic*, and in *flatulent constipation*, asafetida enemata (two to four fluidrachms of milk) are useful and harmless.

### SUMBUL.

Although the U. S. Pharmacopœia defines sumbul as the “rhizome and root of an undetermined plant” it is generally supposed to be derived from the *Ferula sumbul*, a large perennial plant growing in Central and Eastern Asia. It enters commerce in the form of brown pieces, one-half to two inches long and about one inch in diameter. The odor is musk-like, the taste at first sweet, but then bitter, and leaving a sensation of warmth. It depends for its activity upon the presence of *sumbulic* or *angelic acid*, and probably also contains valeric acid.

#### Official Preparations:

Extractum Sumbul. ....	5 to 10 grains (0.3–0.6 Gm.).
Fluidextractum Sumbul. ....	$\frac{1}{2}$ to 1 fluidrachm (2–4 C.c.).

**Therapeutics.**—Sumbul is used for similar purpose as valerian, but is especially valued in nervous states associated with disorders of menstruation.

### HOPS.

The strobiles (fruit) of *Humulus lupulus*, or hop-vine, cultivated in Northern and Middle Europe and in the United States, are soft, greenish cones, one or two inches in length, composed of thin, leaf-like, imbricated scales, having a bitter taste and a heavy narcotic odor. At the bases of the scales is a yellowish powder, official under the name of *Lupulinum*. *Lupulin* is in minute grains, and contains, according to Payen, two per cent. of volatile oil, 10.3 per cent. of bitter principle, and fifty to fifty-five per cent. of resin. Volatile oil of hops is yellowish, and has a strong odor of the drug and an acrid

taste. The bitter principle has been obtained by Lermer in brilliant rhombic columns, of an acid reaction.

#### Official Preparations :

Fluidextractum Lupulini.....	15 to 30 minims (1-2 C.c.).
Oleoresina Lupulini.....	5 to 15 minims (0.3-1.0 C.c.).
Humulus.....	$\frac{1}{2}$ to 1 drachm (2-4 Gm.).

Hops is a bitter tonic and a very feeble narcotic, which has been given to quiet nervous irritability, and to strengthen digestion in *neurasthenia*, and even in *delirium tremens*. In *abnormal sexual excitement* it has been much used, but is of no value. A *hop poultice* is made by moistening with hot water the hops contained, alone or mixed with an equal part of Indian meal, in a gauze bag of the required size and shape.

#### CIMICIFUGA.

The *Cimicifuga racemosa* is an indigenous herbaceous plant, growing abundantly in shady woods, attaining a height of six or seven feet, and readily distinguished by its very large multi-compound leaves and its long-branched spikes of whitish polyandrous flowers, naked when open. The official portions consist of a knotted head, with numerous fine, brittle rootlets; the odor is faint, and the taste bitterish, somewhat astringent and acrid. The nature of its active principle has not been determined. The tendency of the drug to deteriorate on keeping indicates the presence of a volatile principle.

#### Official Preparations :

Extractum Cimicifugæ.....	5 to 15 grains (0.3-1.0 Gm.).
Fluidextractum Cimicifugæ.....	20 to 60 minims (1.2-4.0 C.c.).
Tinctura Cimicifugæ (20 per cent.).....	1 to 2 fluidrachms (4-8 C.c.).

**Physiological Action.**—There have been no cases of poisoning by *cimicifuga*, but large doses produce giddiness, intense headache, general prostration (evidences that it has influence upon the cerebrum), with reduction of the pulse-force and rate, and occasionally vomiting, but the emetic action is never violent. Hutchinson found that large doses acted on frogs as a depressant of the sensory side of the spinal cord, producing complete anesthesia with loss of reflex activity at a time when voluntary movement was still preserved, the development of the anesthesia not being prevented by shutting off access of the poison from the peripheral nerves by tying the arteries of the leg, and both motor nerves and muscles being found after death functionally active. Upon the circulation *cimicifuga* acts as a depressant, producing in the mammal fall of the arterial pressure and slowing of the pulse, and causing finally diastolic arrest of the heart. As the slowing of the pulse is not prevented by previous section of the vagi, and as the isolated frog's heart becomes slow and in a little while paralyzed after direct contact with the *cimicifuga*, it is evident that the drug acts as a direct depressant to the heart-muscle; but.



since Hutchinson found that asphyxia is incapable of causing rise of pressure while the heart is still beating strongly, it is probable that it not only depresses the heart but also the arterial system. Under the influence of the drug the respiration becomes slow and suffers final arrest.

**Therapeutics.**—Cimicifuga was originally proposed by Young in 1831 as a remedy in *chorea*, and in the simple chorea of childhood its value is unquestionable. It must be given until it produces physiological effects, and in most cases the consentaneous exhibition of iron and laxatives materially aids it. We have seen it promptly cure *urticaria* of nervous origin after complete failure of the usual treatment. In acute *inflammatory rheumatism* cimicifuga has been highly recommended, but is at present very rarely, if ever, used. In *chronic bronchitis* it is sometimes employed with asserted benefit when there is free expectoration.

CYPRIPEDIUM is the rhizome and roots of *Cypripedium hirsutum* and *Cypripedium parviflorum*, to which are attributed tonic, diaphoretic, and antispasmodic properties. They are said to contain a volatile oil but no alkaloids.

*Cypripedin* of the drug stores is an impure oleoresinous substance, the dose of which is given as from one-half to three grains. *Cypripedium* is especially recommended for the allaying of functional nervous excitability and in hypochondriasis. The fluidextract, FLUIDEXTRACTUM CYPRIPEDII, may be given in doses of fifteen to thirty minims (1-2 C.c.).

ACETIC ETHER (*Æther Aceticus*) is a transparent, colorless, somewhat fragrant liquid, containing about ninety per cent. of *ethyl acetate*. It has been used to a slight extent in medicine as a stimulant and calmative. It resembles ordinary ether somewhat in its action, but is less volatile and less rapidly absorbed and eliminated. It is capable of producing anesthesia, but is in every respect much slower and less certain in its action than ordinary ether, and is practically of no value. Dose, internally, fifteen minims (1 C.c.).

LACTUCARIUM.—The concrete juice of the *Lactuca virosa*,\* or garden lettuce, occurs as a dark reddish-brown to a light yellowish, hard extract, having a faintly narcotic odor and bitter taste. A peculiar soothing, hypnotic influence has been attributed to it, but its activities are so feeble that in a number of trials with very large doses we have been unable to perceive any effect whatever. According to Fronmüller, *lactucin* is even less active than the crude drug. In France lactucarium is used locally as a narcotic demulcent in the treatment of diseases of the throat.

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\* For a case of reputed poisoning by *Lactuca virosa*, see *Schmidt's Jahrb.*, clxxi. 137.

**Official Preparations:**

- Tinctura Lactucarii (50 per cent.).....1 to 2 fluidrachms (4-8 C.c.).  
 Syrupus Lactucarii (10 per cent.)..... $\frac{1}{2}$  to 1 fluidounce (15-30 C.c.).

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**CINICIFUGA.**

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**LACTUCARIUM.**

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## FAMILY II.—ANESTHETICS.

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THE term *Anesthetics* is here employed as the name of a group of volatile substances, whose vapor has the power of producing loss of consciousness, preceded by or accompanied with loss of sensibility and diminished muscular action. The medical properties of these substances are largely due to their volatility, by virtue of which they are very rapidly absorbed and almost as rapidly eliminated by the mucous membrane of the lungs. As a consequence of this, their action is easily controlled.

A very large number of theories have been brought forward to account for the peculiar effects of anesthetics; of the more important of these theories an elaborate discussion may be found in the tenth edition of this work. There is, however, nothing more mysterious in the action of ether and chloroform upon the nerve-centres than there is in the influence of opium or strychnine upon these centres, the influence of the anesthetic being as certainly direct and vital as is that of any other drug which acts upon human organs or tissues.

The action of anesthetics may be modified by the injection of narcotics. Morphine given hypodermically about half an hour before the exhibition of the anesthetic is said to have a decided effect in prolonging the anesthesia. Chloral administered shortly before etherization certainly causes the first stages of the latter to be much quieter than usual, and also prolongs the narcosis. Some years since Neudörfan introduced into Berlin the use of oxygen gas with chloroform in the production of anesthesia; more recently the method has been revived in America.\* It has even been asserted that the oxygen increased the anesthetic effect of the chloroform. There is not at present writing sufficient evidence, however, of the value of the method.

The chief purposes for which anesthetics are used are to *relieve pain* and to *relax spasm*. To meet the first indication they are employed by surgeons especially; but they are also exceedingly valuable in cases of suffering from disease. It must be borne in mind that their action is transitory and is accompanied by more or less disturbance of the general system, and that consequently they are to be employed only when the pain is exceedingly severe and transient. To relieve pain, anesthetics are used with great propriety during *childbirth*.† In normal labor it is not commonly necessary to produce complete

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\* See *Boston Med. and Surg. Journ.*, 1896, and *New York Med. Record*, 1896.

† We see no reason for believing that anesthesia of the mother seriously influences the child and do not think that much weight can be attached to the assertions of Hofmeier (*Berlin. Klin. Wochenschr.*, 1883, xx. 230) that there is produced an increased elimination of nitrogen in the new-born babe.

anesthesia. When the full effect of either ether or chloroform is induced, there is almost always a weakening, and very often an abolition, of the uterine contractions. The anesthetic should be administered in such quantities as to relieve the pain without decidedly interfering with the muscular spasm. In certain cases this can be done, in others it is impracticable. We have obtained advantageous results in some cases by suspending the pains for about half an hour by means of ether, and then entirely withdrawing the anesthetic. By this treatment the weak, painful, ineffectual efforts of a worn-out, nervous patient may often be converted into regular, successful efforts. The risk of *post-partum hemorrhage* is materially increased by anesthetics, so that it is well to administer, after their use, two drachms of the fluidextract of ergot as soon as the perineum is well distended by the child's head.\* Anesthetics are frequently used in surgery for the purpose of relaxing spasm, as in cases of *dislocation*, *hernia*, etc. In medicine they have been employed in various forms of *convulsions*, and are especially valuable in severe *hysterical convulsions*, in *puerperal eclampsia*, and in *spinal convulsions*; in *epilepsy* they are very rarely called for; in *infantile convulsions* they may be sparingly used when the convulsion itself threatens life. In various *spasms of the excretory ducts or canals*, and especially during the passage of *calculi*, they act very favorably, both by relieving pain and by producing relaxation. In *asthma*, and in *spasmodic stricture of the œsophagus*, as in all other cases of oft-repeated spasm, they should be administered only to meet temporary indications, as their habitual use is deleterious.

### NITROUS OXIDE.

Nitrogen Monoxide ( $N_2O$ ) is a colorless, almost inodorous, gas, of a sweetish taste. It is a very active supporter of combustion. Water absorbs nearly its own bulk of it. It is made by the distillation of ammonium nitrate, which resolves itself into the gas and water. Nitrous oxide gas is now supplied in condensed form. In making nitrous oxide the temperature should never be allowed to rise above  $482^\circ F.$ , for fear of generating *nitric oxide*.

**Physiological Action.**—The inhalation of pure nitrous oxide gas is followed in from a half to three minutes by unconsciousness, which usually comes on quietly, but is sometimes preceded by hilarious, erotic, or pugnacious excitement. During the anesthesia the face presents a bloated, swollen, intensely livid appearance.

The question whether nitrous oxide produces anesthesia through inherent properties of its own, or whether it acts simply by shutting off oxygen, has been much discussed. The intoxicating effects of mixtures of nitrous oxide and oxygen, although complete anesthesia may not result, show that the gas has a direct action on the brain.

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\* Deaths from anesthetics are very rare during parturition, but have occurred. (See C. B. Vanzant, *Cincinnati Lancet*, 1893, xxx.)



Moreover, Paul Bert has shown that a mixture of nitrous oxide and oxygen, under pressure, will produce complete anesthesia. For these and other reasons it is, to-day, generally conceded that nitrous oxide is capable of producing anesthesia by virtue of its own inherent action on the nerve-centres. Nevertheless, the narcosis ordinarily produced is due not only to the nitrous oxide but also in part to asphyxiation. The evidence on both sides of this discussion is briefly summarized in small type below.

It is well established that nitrous oxide will not support life. A taper will burn in it, it is true, but the liberation of oxygen is due to the high heat, and at the temperature of the body nitrous oxide is a stable compound.

In 1864 Ludimar Hermann, as the result of his experiments, came to the conclusion that the addition of oxygen to nitrous oxide puts an end to its anesthetic properties, and that it acts simply as an asphyxiant. In 1873 Jolyet and Blanche arrived at a like opinion as they found that animals breathing an air containing sixty to eighty per cent. of nitrous oxide and twenty to forty per cent. of oxygen are unaffected; analyses of the blood of two dogs yielded the following results:

No. 1. Conscious.		No. 2. Unconscious.	
Carbonic acid.....	46 per cent.	Carbonic acid.....	36.6 per cent.
Nitrous oxide.....	29 per cent.	Nitrous oxide.....	34.6 per cent.
Oxygen.....	19.7 per cent.	Oxygen.....	3.3 per cent.

The statements of the French observers just quoted have been abundantly corroborated by the observations of various subsequent investigators. Colton, Elihu Thomson, and H. C. Wood have separately and repeatedly demonstrated that animals will live no longer in nitrous oxide than they will in an atmosphere of hydrogen or nitrogen, or even in a vacuum. In a long series of experiments, H. C. Wood determined that the introduction of minute quantities of oxygen into nitrous oxide prolonged the time necessary for the production of anesthesia in direct proportion to the percentage present, ten or even eight per cent. of oxygen suspending entirely the anesthetic action of nitrous oxide gas upon the dog. The average time required for the production of anesthesia was nearly doubled by the addition of three per cent. of oxygen, and increased more than twelvefold by the use of five per cent. of oxygen. Thomson asserts that the inhalation of pure nitrogen produces symptoms similar to those of nitrous oxide narcosis. In conformity with this are the researches of C. A. MacMunn and Amory; the former observer finding that when an animal is killed by nitrous oxide the arterial blood gives only spectrum lines of reduced hemoglobin, while after death from chloroform the lines of oxyhemoglobin are very apparent.

H. C. Wood found that the inhalation of nitrous oxide is usually followed by a rise of the arterial pressure, accompanied by a great disturbance of the pulse; the pulse at first becoming irregular and tumultuous, but by and by settling, so that when anesthesia is complete the pulse-wave is remarkably large and full and the rate very slow. The rise and fall of the arterial pressure in nitrous oxide anesthesia was found to vary remarkably, not only in different inhalations, but at different periods of the same inhalation. Amory has found, in experiments upon the dog, that there is, during the anesthesia, increased blood-pressure in the cerebrum, with stasis in the capillaries. These results show that the circulatory phenomena produced by nitrous oxide resemble those of mechanical asphyxia as closely as could, *a priori*, be expected.

Martin Goldstein found that when he put frogs in an atmosphere of pure nitrous oxide they became motionless, with a complete loss of the reflexes, in fifteen minutes; while when they were put in an atmosphere of nitrogen or some other indifferent gas they preserved their irritability for some hours. It is known that while the nervous system of the mammal requires for its activity the presence of

oxygen, the nervous system of the frog remains functionally active for some hours after all circulation—that is, after all carrying of oxygen to it—has ceased.

Believing that if he could increase the amount of nitrous oxide in the blood he could get an anesthetic action from it, Paul Bert experimented by exposing the animal in a chamber having air so compressed that the pressure was at least that of two atmospheres, and found that under these circumstances he could obtain anesthesia with a mixture of eighty-five per cent. of nitrous oxide and fifteen per cent. of oxygen, but that when nitrogen was substituted for nitrous oxide no anesthesia was produced. Bert's method was for a time employed for the purposes of surgical anesthesia in Paris and in some other capitals of Europe, the clinical records showing that it is possible to produce anesthesia with the gas in the proportion named above. Practically, however, the necessary apparatus was found to be too cumbersome and expensive for use. In 1881 Kliekovich, of St. Petersburg, too with alleged success in parturition Paul Bert's mixture of gases without pressure.

In 1891 Van Arsdale found that it was possible in rare cases to produce anesthesia in the human being with mixtures of oxygen and nitrous oxide in the proportion of fifteen to eighty-five per cent., and that in many cases a mixture in the proportion of ten to ninety per cent. would produce a moderately complete anesthesia without cyanosis.

In a research extending over three years, F. W. Hewitt corroborated the assertions of Van Arsdale, finding that it is possible, in some cases at least, to produce deep and satisfactory anesthesia, without obvious asphyxial manifestations, by mixtures of nitrous oxide and oxygen containing even as much of the oxygen as is present in our atmosphere. George T. Kemp made a series of experiments, some of which seem to be very decisive. Thus, an animal having been anesthetized with nitrous oxide, a slit in the canula was adjusted so that it let in just sufficient air to keep the animal alive and anesthetized. When nitrogen was substituted for nitrous oxide, the amount of air remaining the same, the dog gradually came out of his anesthesia. Experiments with the blood showed that, though at times perfect anesthesia existed with as high a percentage of oxygen in the blood as 16.8, it usually was 8.5, and sometimes not until the percentage was reduced to 7.9. For reasons given in his paper, which we cannot go over here, Kemp believes that with this amount of oxygen metabolism remains about normal, a conclusion, however, which the evidence he brings forward hardly proves.

If nitrous oxide, as the evidence at present indicates, is capable of producing unconsciousness by virtue of its inherent properties, it must act upon the cerebrum, but it is remarkably inert in regard to other portions of the organism. The chief evidence as to its influence upon the spinal cord is that of Goldstein, that it diminishes the reflexes in frogs. That its action on the spinal cord is very feeble seems to be shown by the fact, which has been repeatedly asserted, that in human beings the conjunctival reflexes often persist after deep anesthesia has been produced.

The experiments of Waller and of Amory show that nitrous oxide does not affect the motor nerve trunks. Ulbrich believes that it produces alterations in the blood, but Hermann, Jolyet and Blanche, Goldstein, MacMunn, Buxton, and Halliburton are in accord with Kemp in asserting that it does not make any compound with hemoglobin. Further, Kemp is in accord with H. C. Wood's experiments in showing that it has no definite influence upon the heart or the arteries.

**Therapeutics.**—Of all the anesthetics, nitrous oxide is the safest. It is probably administered to more than seven hundred and fifty

thousand persons yearly, and yet only four recorded deaths are certainly attributable to it.\* The opinion of Cartwright and of W. Ottley, that in cases of heart disease permanent increase of the cardiac weakness is caused by nitrous gas inhalation, is not established. The final fall of blood-pressure produced by the gas was found in the experiments of H. C. Wood to be due to paralysis of the vaso-motor apparatus, probably of asphyxial origin, and death always occurred from respiratory paralysis, the heart continuing to beat powerfully after respiration had ceased and the arterial pressure had fallen very low. Even when alarming symptoms occur during nitrous oxide anesthesia, the results are very rarely disastrous, because the loss of function has been due, not to the presence of a poison, but to the absence of oxygen, and although the paralysis may be complete, the life-power sleeps before it dies, and is ready to react to oxygen. *Immediate artificial respiration* is the *one remedy* for the treatment of alarming symptoms during nitrous oxide asphyxia.

In diseases of the kidney nitrous oxide is probably far safer than any of the liquid anesthetics, since in the experiments of Thomson and Kemp it was found to have no other effect upon the kidneys than that which it exerted upon the general circulation. Experience has not confirmed the assertion of Lafont, that nitrous oxide anesthesia is prone to be followed by miscarriage, chlorosis, and epilepsy. His especial warning against the production of diabetes mellitus, and his statement that glycosuria may be produced by the drug in the dog, remain unconfirmed by clinical or experimental evidence, although a well-known Philadelphia surgeon persistently attributed his own fatal diabetes to the use of nitrous oxide. In experiments made by George S. Woodward and Alfred Hand in the laboratory of the University of Pennsylvania it was found impossible to produce glycosuria in the dog. On account of the high blood-pressure with venous stasis which occurs during nitrous oxide anesthesia, atheroma or other diseases of the arterial walls should be considered a contra-indication to the use of the gas, and fatal apoplexy† has occurred during or immediately after its administration.

**Administration.**—The difficulty with the practical use of nitrous oxide for other than the brief anesthesia required in teeth extraction and other forms of minor surgery has been the extreme fugaciousness of the anesthesia, as well as the asphyxial symptoms always present. It is affirmed that these difficulties are overcome by the consentaneous use of oxygen with the gas. Undoubtedly the asphyxial symptoms are greatly lessened, but the allegation that the period of recovery after the withdrawal of the gas is distinctly prolonged has not, in our experience, been sustained. In various cases we have noticed the return to consciousness as complete in from twenty-eight to forty

\* Not including the case reported in the *Dental Cosmos*, June, 1872. (See *Brit. Journ. Dent. Sci.*, Feb. 1873; *Brit. Med. Journ.*, 1877, i. 460; *Ibid.*, 1883, ii. 729; *Dent. and Surg. Microcosm*, Oct. 1895.) In one of these cases the result is said to have been due to syncope.

† See *Dental Cosmos*, 1890; also *Therap. Gaz.*, 1896, xii.



seconds. With great care in the administration of the mixed gases, the anesthesia can be, it is true, almost indefinitely prolonged, but the danger of recovery at any moment is great. It is common for operators to vary the percentage of oxygen according to the appearance of the patient, often giving first pure nitrous oxide and adding oxygen without any definite measurement when the asphyxial symptoms set in; watching the effect of the oxygen and increasing or lessening it according to the facial expression of the patient. Matthew H. Cryer, of the University of Pennsylvania Dental Faculty, states that the apparatus prepared in London according to Hewitt's plan is impracticable owing to the fact that an easy reflux is afforded for the two gases into each other, and has worked out an apparatus which seems to be satisfactory and is not over-cumbersome. The method is certainly a distinct advance, in that it enables the operator at any moment to have the subject breathe pure oxygen if disagreeable symptoms occur.

Nitrous oxide is sometimes used in conjunction with ether, the primary anesthesia of nitrous oxide allowing the patient to pass under the ether without the unpleasant excitement. Le Breton is probably correct in his belief that this method is safer than ether alone, because of the smaller amount of ether required.

### ETHER.

*Ethyl oxide*  $[(C_2H_5)_2O]$  is a colorless, volatile liquid, obtained by the dehydration of alcohol by sulphuric acid. It is very inflammable, as is also its vapor, which is two and a half times heavier than air. It is freely soluble in alcohol, and is itself a powerful solvent. Its odor is strong and peculiar; its taste is hot. Its specific gravity, when pure, is 0.713, and its boiling point  $95^\circ F$ . Ether of the U. S. Pharmacopœia contains ninety-six per cent. of ethyl oxide, and should boil "when a test-tube, containing some broken glass and half filled with it, is held for some time closely grasped in the hand."

#### Official Preparations:

Æther.....	15 to 60 minims (1-4 C.c.).
Spiritus Ætheris (32 per cent.).....	$\frac{1}{2}$ to 2 fluidrachms (2-8 C.c.).
Spiritus Ætheris Compositus [Hoffman's Anodyne] (Ether 325, Ethereal oil * 25, Alcohol 650).....	$\frac{1}{2}$ to 2 fluidrachms (2-8 C.c.).

Although ether had been known chemically for many years and had even been employed in the treatment of pulmonary affections the credit of introducing it as a general anesthetic belongs to

\* When alcohol is distilled with an excess of sulphuric acid there is found a substance commonly known as *heavy oil of wine*; this when mixed with an equal volume of ether constitutes *Oleum Æthereum* of the U. S. Pharmacopœia.

Heavy oil of wine is a substance of little power, but Hare has shown that large doses are primarily stimulant to the vaso-motor centres and later, if the quantity is sufficient, dilate the vessels and weaken the heart. It is improbable that the presence of this compound affects the action of Hoffman's anodyne, whose virtues as a carminative and calmative are due chiefly to the ether.



W. T. G. Morton, a Boston dentist, who employed it in his practice in 1846, and later called it to the attention of Dr. Warren, who performed the first surgical operation under artificial anesthesia in the same year.

**Physiological Action.**—Locally, ether is a violent irritant; it is absorbed with rapidity through the mucous membranes both of the lungs and of the gastro-intestinal tract. When taken freely it is eliminated largely unchanged by the lungs.

Upon the lower animals ether acts as upon man, and it has been shown by Claude Bernard that the most primitive infusoria are susceptible to its influence.

**Nervous System.**—Both in man and the lower animals the cerebral functions are the first to be affected by ether; the order of the involvement is—first the cerebrum, next the sensory centres of the cord, next the motor centres of the cord, next the sensory centres of the medulla oblongata, and finally the motor centres of the medulla oblongata. The nerve trunks can be paralyzed by the direct application of ether vapors, but this probably does not occur in the living animal.

According to the experiments of H. C. Wood, Jr., when the ether is given in such a manner to the dog as to avoid all violence of administration, and in minute dose, the first positive indication of the loss of intellection is failure of the perception and interpretation of sound, the sense of sight lasting somewhat longer. Loss of coordination and loss of motor power, though with a continuation of movement, are the next phenomena. It was further demonstrated in these experiments that there is a stage of ether narcosis in which the sensibility is distinctly lessened, although no motor changes are demonstrable. This affords confirmation of the early experiments of Flourens, who found that the order in which during etherization the power of responding to pricking is lost was, first, in the posterior or sensory portion of the spinal centres; second, in the anterior or motor portions of the spinal cord; and, third, in the medulla oblongata. Longet has confirmed this order, except that by using powerful galvanic currents he was able, even in the deepest narcosis, to get a response from the anterior portion of the cord.

Wright has demonstrated histological changes in the pyramidal cells of the nervous centres due to the administration of ether or chloroform. The more prolonged the exposure to the anesthetic, the slower is the return to the normal.

Waller found that if he brought dilute ether or chloroform vapor in direct contact with a motor nerve, that nerve lost its power of transmitting electrical impulses. If the vapor had not been too concentrated, the nerve recovered its function after removal of the anesthetic. The recovery after chloroform was less rapid than after ether. If the observations of Longet and Serres be correct, the sensory nerve-fibres are more susceptible to the influence of ether than are the motor. They found it possible, however, by the direct application of ether to a nerve, to produce a condition in which pinching the nerve below the point of application caused no pain, although voluntary movement was preserved, and galvanization of the nerve trunk above the point of application induced spasms in the tributary muscles,—i.e., the power of conducting an impulse downward was preserved, that of conducting it upward was lost. By a longer application of the anesthetic the function of the efferent as well as of the afferent fibres was abolished, temporarily at first, but, if the application were persisted in, permanently.

Conly found that in animals killed by ether, chloroform, or chloral, the motor nerves and muscles preserve their function longer than in animals killed by sudden violence. Nevertheless, F. S. Locke found that in the frog, at least, the muscles

are directly affected by etherization; there being not only a lessening of the height of the contraction under stimulation, but also an alteration in its form.

Upon the motor system of organic life ether certainly acts, but much less energetically than upon the voluntary system. Thus, after death from ether the vermicular movements of the intestine, although less active than normal, are very rarely, if ever, entirely absent.

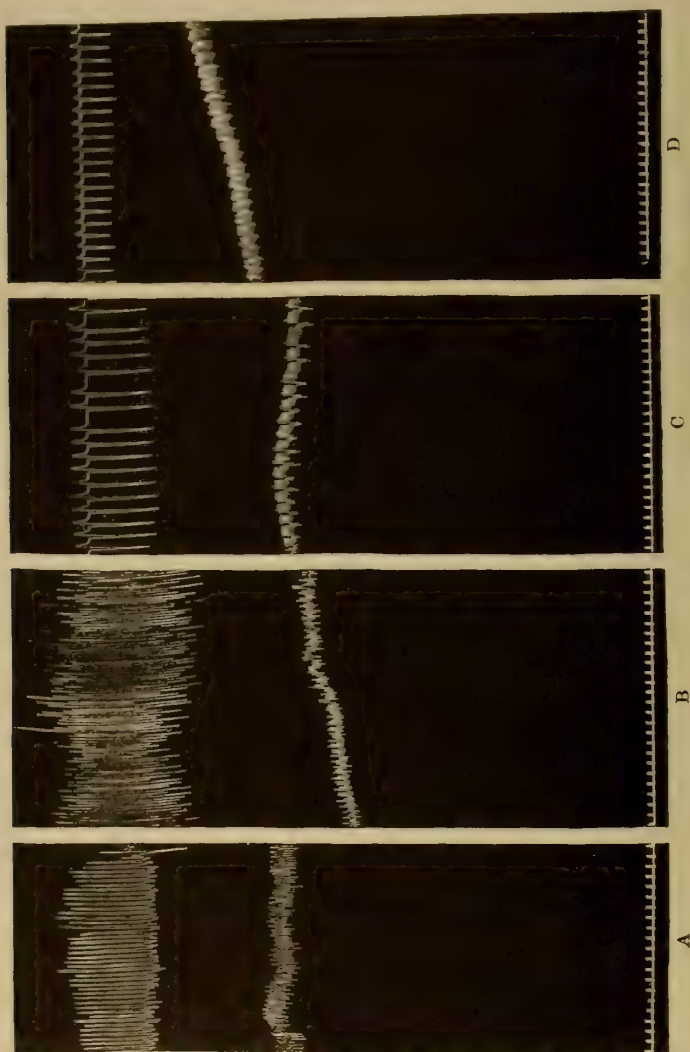


FIG. 1.—SHOWING THE EFFECT OF ETHER ON THE CIRCULATION AND RESPIRATION.  
A.—Normal. B.—Stage of excitement. C.—Stage of anesthesia. D.—Beginning of toxic action. Note that the blood-pressure is high despite the dangerous depression of respiration. Time marker indicates two seconds.

*Circulation.*—The first effect of ether is usually to cause a rise in the arterial pressure, which may be maintained even through a prolonged ether narcosis, and may continue until manifest failure of respiration; usually, however, it is after a time succeeded by a fall of pressure. Blauel found, in tonometrical studies upon man, that during ether anesthesia the pressure is raised in seventy-nine per

cent. of the cases, not affected in nine per cent., lowered in twelve per cent. What evidence we have upon the subject indicates that the primary action of ether upon the heart is that of a stimulant, though later if in sufficient amount it undoubtedly acts as a cardiac depressant; that this depressing action is feeble, is shown by the experiments of Tunnicliffe and Rosenheim, who found that in the excised mammalian heart two per cent. of ether in the blood did not stop the heart.

The rise of blood-pressure appears, however, not to be entirely cardiac, since Sansom found that the vessels of the frog's web are thrown into a persistent spasm by the inhalation of ether; and Bowditch and Minot conclude as the result of their experiments that in the mammal the drug first stimulates, afterwards depresses, the vaso-motor centres.

*Blood.*—It is frequently asserted that ether when added to blood coagulates it. A. Schmidt, however, states that the coagulation is due to ozone which has been generated in the ether, since freshly distilled ether does not coagulate albuminous substances.

The researches of Wittich and of A. Schmidt have shown that when ether is added to the blood of horses, cats, or rats, the red corpuscles disappear in a very short time, and, as their stroma cannot be demonstrated by the aid of reagents, this disappearance is due to its solution. The oxyhemoglobin thus set free is dissolved in the serum, but the presence of the ether soon causes it to crystallize. There is no proof that these changes occur to any extent when ether is inhaled; and the usual rapid recovery from the effects of the anesthetic indicates that there is no profound alteration of the blood.

An imperfect study by Harley of the effect of ether on the gases contained in drawn blood indicates that ether does not exert much influence upon their proportional amounts. It is, however, quite possible that a more thorough investigation would give a different result.\*

**SUMMARY.**—Locally ether is a violent irritant. In excess it probably depresses all higher tissues, but it especially acts upon, first, the cerebrum, next upon the sensory, and then upon the motor side of the spinal cord. It usually produces death by asphyxia, due to depression of the respiratory centres. Its first action upon the circulation is that of a stimulant to the heart, and perhaps also to the vaso-motor centres. The large dose finally depresses both heart and blood-vessels.

**Therapeutics.**—For a discussion of the use of ether as an anesthetic, see *Practical Anesthesia*, page 37.

Ether has been administered by the mouth in the treatment of *colic*; for this purpose the compound spirit of ether is usually to be preferred. It has also been employed as an anthelmintic against the

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\* For literature, cases, and discussion, see Schulz, *Deutsch. Militär. Zeitsch.*, 1903, xxxii.



*tapeworm*, but is inferior to other remedies. It is occasionally employed in the treatment of various nervous conditions, as *neuralgia*, *hysteria*, *hiccoughs*, and the like.

Ether has also been used as a cardiac stimulant in the treatment of *syncope*, *shock*, and other conditions in which a rapidly acting remedy is required; for this purpose it is usually given hypodermatically, its value, however, is doubtful.

When ether is swallowed, it produces a sense of strangulation and choking which seriously interferes with its use. For this reason, it is often given in capsules, or in ice-cold water. Probably large doses are best administered by putting them, mixed with an equal amount of brandy, on finely cracked ice before drinking.

### CHLOROFORM.

Chloroform, which was discovered in 1831 by Samuel Guthrie, of Sackett's Harbor, New York, has the formula  $\text{CHCl}_3$  and is generally regarded as a trichlormethane. It is produced by the action of chlorine upon alcohol. It is a colorless, limpid, and neutral fluid, with a specific gravity of 1.476. Although practically non-inflammable, it can be made to burn with a greenish flame. Its taste is hot and sweetish, its odor fragrant and peculiar. It is soluble in alcohol and in ether, but almost insoluble in water. The U. S. Pharmacopœia requires that chloroform should contain, by weight, 99 to 99.4 per cent. of absolute chloroform and 0.6 to 1 per cent. of alcohol.

#### Official Preparations:

Chloroformum.....	15 to 30 minims (1-2 C.c.).
Spiritus Chloroformi (6 per cent.).....	1 to 2 fluidrachms (4-8 C.c.).
Emulum Chloroformi (4 per cent.).....	2 to 4 fluidrachms (8-15 C.c.).
Aqua Chloroformi (Saturated Solution, about $\frac{1}{2}$ per cent.).....	4 fluidrachms (15 C.c.).
Linimentum Chloroformi (30 per cent.)....	External Use Only.

**Physiological Action.**—*Local Effects.*—Although somewhat of an anesthetic, chloroform applied locally is a powerful irritant. On the skin it produces redness and burning; if the evaporation be restrained vesication will be induced by it. Taken into the mouth, it causes a burning sensation, and, when swallowed, a sense of warmth in the stomach. According to both Strassmann and Salkowski it is an active germicide. The latter author as well as Bertels finds that it checks the activity of pepsin and other ferments.

*Absorption and Elimination.*—Chloroform is rapidly absorbed through the mucous membrane of the respiratory and digestive apparatus. Its exact fate in the body is at present unknown. It is certainly eliminated, at least in part, unchanged in the expired air after administration by the mouth (Benedicenti); and after its inhalation has been detected by Fubini, by Siolfatti and by Nicloux in the urine. It is probably, however, in part decomposed in the system, since A. Zeller has found that the chlorides of the urine are nearly doubled by its inhalation.



The vapor of chloroform, when inhaled, produces symptoms seemingly similar to those induced by ether, except that the choking sensations are absent, and that the stage of excitement is generally, but not always, shorter and less violent than is that of etherization.

*Nervous System.*—The experiments of Holmgren, Kratschmer, H. C. Wood, Jr., and others have demonstrated that the action of chloroform upon the nervous system is entirely parallel to that of ether (see page 27), the difference being simply one of intensity of power. In practical anesthesia the stage of excitement is usually much less severe with chloroform than with ether, but, according to H. C. Wood, Jr., this hyperexcitation depends largely upon the ether vapor being too concentrated; when the anesthesia was induced in animals slowly with a very small percentage of ether in the air, the stage of excitement was greater with chloroform than with ether. The motor disturbances seen early in chloroformization, as in etherization, have been supposed to indicate a condition of spinal stimulation, but have been shown by Bert to be of purely psychical origin.

Bernstein found that there was no perceptible difference in the conducting power of the two ischiatic nerves of a frog chloroformed after one of its iliac arteries had been tied.

*Circulation.*—When chloroform vapors are inhaled in a concentrated form the first effect is a marked slowing of the pulse and rapid fall of blood-pressure. Dogiel believes that this is due to a stimulation of the inhibitory centres, because he has found that it does not occur after section of the vagi. Death has frequently occurred from chloroform after the inhalation of a few whiffs of vapor. The theory was suggested many years ago that the cause of cardiac arrest is irritation of the respiratory mucous membranes, producing a fatal cardiac inhibition; a conclusion which reached confirmation in the observations of Embley, who found that when inhalations of chloroform of the strength of two per cent. and upward have been given and the blood-pressure has fallen, stimulation of the vagi with the faradic current fatally inhibits the heart. The after-increase in the rapidity of the pulse appears to be due, at least in part, to paralysis of the inhibitory centres, upon which chloroform seems to act as upon the oculo-motor centres, producing in them at first excessive functional activity, but afterwards functional paralysis. Both Kratschmer and Knoll have noticed in rabbits, when either ether or chloroform is inhaled through the nose, a momentary rise of arterial pressure corresponding to an arrest of respiration, and, like it, evidently produced by irritation of the peripheral trigeminal branches.

As was first proved by the English Chloroform Committee, after the first half-minute of the inhalation of chloroform, as ordinarily administered, there is a progressive lowering of the arterial pressure. This has been confirmed by all observers on the lower animals, and Blauel has shown by tonometrical experiments that the same phenomenon occurs in man. There has been much dispute as to the cause of this fall,—whether it is of cardiac or vascular origin. There is

to-day, however, no longer any room for doubt but that chloroform is a direct depressant to the heart-muscle. Indeed there is strong evidence that, in moderate quantities, it is stimulant to the vaso-motor centres although after large doses the vaso-motor mechanism is completely paralyzed.

Injected into the jugular vein, chloroform instantly arrests the heart's action and destroys its muscular irritability.\* Even the vapor of chloroform, when locally applied to the exposed heart, paralyzes it. When artificial respiration is maintained, the effect of chloroform is very apparent. By a very ingenious series of experiments, MacWilliam has proved that very early in chloroform anesthesia there is a marked diminution of the force of the auricular and the ventricular beats, accompanied by dilatation of the cardiac chambers, due to the direct influence of the chloroform. Tunnicliffe and Rosenheim, using the method of Locke, found that 1 to 25,000 in the blood of chloroform notably affected the heart, and Schafer and Scharlieb have reached similar results. In the experiments of E. H. Embley, made in the method of Hering upon the mammalian heart isolated from nervous and respiratory influences, it was determined that the heart is so sensitive to the vapor of chloroform that 0.8 per cent. in the blood will produce paralysis in sixteen minutes, and with two per cent., arrest occurs in one minute and twenty-five seconds.

In an elaborate series of experiments, Sherrington and Sowton found that the heart-muscle rapidly takes up chloroform from the blood-vessel, the tension or amount of the chloroform in the muscle depending not upon the length of time of exposure but upon the percentage of chloroform in the fluid circulating in the coronary arteries; it was further determined that the presence of the chloroform in the muscle is accompanied by depression of function, and that when the percentage is great muscular paralysis occurs. The thought naturally arises from this research that sudden death may occur during chloroform anesthesia from the momentary sudden increase of the percentage of chloroform in the blood.

The only experiments with which we are acquainted, to which any weight should be attached, as indicating that chloroform primarily paralyzes the vaso-motor centres, are those published as long ago as 1874 by H. P. Bowditch and C. S. Minot. In these experiments, which were made upon curarized animals, "irritation of the saphena nerve caused a much less marked rise of blood-tension than when the anesthetic was not used. Sometimes there was absolutely no rise of tension to be observed, while at other times the rise was from one-third to one-half that produced by the same irritation on an animal not subjected to the action of chloroform." Further, compression of the carotid in the chloroformed animal did not cause the customary spasm and rise of arterial pressure.

It must be remembered that chloroformization interferes with the functional activity of the sensory side of the nervous system, so that an impulse produced by irritation of the sensitive nerve fails to reach the vaso-motor centres in full force. In many of the experiments of Bowditch and Minot, irritation of the saphenous nerve produced distinct rise of pressure, showing that the vaso-motor centre was not paralyzed, though the arterial pressure had fallen very distinctly.

On the other hand Sansom and Harley state that there is a spasm of the small vessels, which can be readily seen to occur in the web of the frog during chloroformization. Not until the third stage is reached, according to these authors, do the vessels relax into dilatation. If these observations be correct, chloroform first stimulates and afterwards depresses the vaso-motor centres. Confirming this are the important experiments of Gaskell and Shore, who find that the local application of chloroform to the medulla or its injection into the cerebral artery produces an immediate rise of blood-pressure, usually accompanied by a slowing of the heart, which is followed by a fall of pressure so soon as the chloroform is able to diffuse itself throughout the circulation. Gaskell and Shore further so connected the

\* Glover (*Edinb. Med. Journ.*, 1842), Gosselin (*Arch. Gén.*, 1848), Anstie, and H. C. Wood.

carotid arteries and jugular vein of an animal (A) with the similar vessels of a second animal (B) that the brain of A was fed exclusively with blood from B. It is plain that chloroform given to B would reach the brain of A but would not reach the heart of A. Under these circumstances it was found that chloroform administered to B produces rise of blood-pressure in A. In a second series of experiments the blood-vessels of A were so connected with those of B that when chloroform was administered to B it reached the heart of A and all other portions of the body except the brain. When this was the case, chloroform given to B produced an immediate fall of pressure in A without there having been any rise. In other words, when chloroform reached the vaso-motor centres and not the heart, it caused rise of arterial pressure; when it reached the heart and not the vaso-motor centres, it caused fall of pressure. In accord with the results of Gaskell and Shore, it has been found by Embley that the local application of chloroform to the vaso-motor centres produces rise of the arterial pressure, which is presumably due to stimulation of the vaso-motor centres. In common with other observers, Embley found that later in the chloroformization there is a vascular paralysis which he believes to be due to a direct action of the chloroform on the muscles of the vessels.

*Respiration.*—So soon as psychical excitement has passed off, or, at first, if there be no such excitement, the respirations may be rendered slower by chloroform, but after a time they are generally quickened, and as the inhalation is persisted in they become more and more shallow, irregular, and distant, and finally cease. In 1870 Paul Bert asserted that during chloroformization there is more than the normal percentage of oxygen in the blood, but in 1885 he affirmed that there was less than the normal percentage. There does not seem to be much doubt that the results of L. G. de Saint-Martin are correct, —namely, that while (probably on account of excessive respiration from excitement) in the beginning of chloroformization there is sometimes hyperoxygenation of the blood, the rule during full anesthesia is decrease of the oxygen of the blood with increase of the carbonic acid.

*Blood.*—As was first demonstrated by Harley, five per cent. of chloroform in the blood destroys the red corpuscle with a final deposition of crystals of oxyhemoglobin.

Boettcher was, we believe, the first to study these changes closely. The first alteration noticeable in the red blood-disks is a diminution of their size, which A. Schmidt and F. Schweiger-Seidel assert to be due to contraction, because when blood is treated with water until the red globules disappear, and carbonic acid gas is passed through the liquid until they reappear, on the addition of chloroform the sharply contoured bodies will be seen to undergo marked contraction. As was first shown by Boettcher and confirmed by Schmidt and Schweiger-Seidel, chloroform alone produces no other alteration than contraction in the red blood-disks; if, however, air be admitted to blood containing chloroform, the corpuscles rapidly disappear, dissolving in the serum, out of which, after a time, oxyhemoglobin crystallizes. Both of the authorities quoted believe that the latter changes are due to oxidation. Boettcher states that chloroform-vapor mixed with air converts enough of the oxygen of the latter into ozone to react with iodized starch-paper; and Schmidt and Schweiger-Seidel have found that an excess of carbonic acid in the blood interferes with the changes caused by chloroform. The facts just noted indicate that the blood changes are the result of simple oxidation, but the studies of F. Krüger show that chloroform, at least outside of the body, produces a series of chemical changes in the hemoglobin.



How far, during ordinary narcosis, chloroform causes changes in the blood is uncertain. A very sensitive test of the destruction of the red disks in the body is found in the production of icterus; icterus following chloroformization is very rare, but the assertion of Frerichs that it does occur is correct.

Bernstein and Leyden have found traces of bile-pigment in the human urine after chloroform-narcosis; while Nothnagel detected bile coloring-matter in the urine of rabbits after subcutaneous injection of chloroform or ether. Husemann intimates, on what authority we do not know, that after anesthesia bile-acids (the precursors of icterus) appear in the urine; but Kappeler, in twenty-five cases of chloroform-narcosis, was not able to obtain a trace of biliary coloring-matter. Sokolovski asserts that the first few hours after chloroformization there is a decrease of the immature white blood-corpuscles, with an increase of the mature white blood-corpuscles, followed by gradual return to normal.

*General Nutrition.*—That chloroform affects the general nutrition of the body is demonstrated by the wide-spread fatty degeneration which sometimes follows long-continued narcosis produced by it (see page 50), as well as by the observations of Strassmann, who found that a pronounced increase of the nitrogenous elimination follows chloroform-narcosis, an increase which would seem to be directly due to the anesthetic, since Salkowski demonstrated that chloroform-water given to dogs distinctly increases the destruction of nitrogenous substances in the body without producing narcosis.

**Therapeutics.**—For a discussion of the use of chloroform as an anesthetic, see *Practical Anesthesia*, p. 37.

When administered by the mouth in sufficient quantity, chloroform produces symptoms similar to, but much more permanent than, those which it causes when inhaled. It is, however, very rarely, if ever, used in this way for its constitutional effect, but is sometimes of advantage in severe *neuralgia*. When for any reason quinine cannot be administered in an *ague*, a sufficient dose of chloroform (one-half to one fluidounce) to produce a mild narcosis, just before the expected time for the recurrence of the chill, will often abort it. Chloroform by the mouth has been also highly recommended as a vermifuge in cases of *tapeworm*, but is of doubtful value.

When chloroform is taken into the stomach, a considerable portion of it is, without doubt, evaporated, so that the intestinal canal becomes filled with the vapor. Chloroform, therefore, when so placed, exerts both a local anodyne and a stimulant carminative action. For this reason it is valuable in ordinary *colic* and in *colica pictonum*.

Externally, as a rubefacient and anodyne, chloroform is very largely combined with other substances into liniments, which are especially useful in cases of *chronic neuralgic* or *rheumatic pains*.

The deep injection of half a drachm of chloroform has been recommended very strenuously by Bartholow in obstinate *neuralgia*, and has found some favor in France. In the only case in which we have tried it, one of trigeminal neuralgia, the local symptoms caused by it were so severe as to imperil the life of the patient.



**Toxicology.**—Poisoning has been produced by the swallowing of chloroform. The symptoms induced have been stupor, with contracted, or, in later stages, dilated pupils, and a stertorous respiration, which finally becomes very irregular, shallow, and often distant. The amount necessary to destroy life probably varies greatly, but, according to L. Lewin, a single fluidrachm has produced death. In some cases\* the fatal result has occurred from secondary gastritis many days after taking the medicine; and not rarely violent gastritis with jaundice apparently from inflammation of the gall-ducts has been produced. Recovery has occurred after the ingestion of three fluidounces without vomiting;† also five fluidounces. After the evacuation of the stomach, by the stomach-pump, the treatment should be similar to that employed to combat the accidents of chloroform anesthesia (see p. 46). Death may occur during the narcosis, or the patient may survive this and perish from inflammation of the trachea, œsophagus, and stomach, caused by the local action of the chloroform.

The recognition of chloroform as the probable cause of any given death cannot be based upon the post-mortem appearances. Indeed, the latter are of no value in deciding such a question. The anesthetic may, however, be recovered by distillation of the lungs and blood within a certain period of time after death. As to the length of this time, so far as we are aware, no investigations have been made.

**Criminal Relations.**—Experiments made at the Philadelphia Hospital and confirmed by Dolbeau and by Paugh have proved that persons sound asleep may be chloroformed without being awakened. Anesthesia cannot, however, be produced in any one partially awake, or even sleeping lightly, without his or her knowledge.

Quite a number of professional men have been accused, and some convicted on the charge, of committing rape on females in whom they had induced anesthesia. No doubt the women believed that they had been violated; but it is certain that in many of the cases they mistook for the real act the subjective erotic sensations induced by the chloroform or ether. The valuelessness of the testimony of persons as to occurrences during the time of their intoxication with anesthetics should be recognized in law as a governing principle of evidence.

### ETHYL CHLORIDE.

*Ethyl Chloride* (*Æthylis Chloridum*) ( $C_2H_5Cl$ ) is a colorless, extremely volatile liquid of specific gravity (at  $0^\circ C.$ ) of 0.918, boiling at  $12.5^\circ C.$  On account of its volatility, it has been much used under various names to produce local anesthesia by freezing. Recently ethyl chloride has been employed as a general anesthetic. It acts very rapidly and recovery occurs abruptly on removal of the drug. It was partially studied physiologically in 1892 by Wood

\* N. Y. M. R., July 11, 1885.

† B. M. J., 1882, ii. 776.

and Cerna, who found that it produced an amount of circulatory depression disproportionate to its anesthetic properties. In Lebet's experiments upon rabbits, the intravenous injection was found to produce great circulatory depression. Embley finds that the action of ethyl chloride is very similar to that of chloroform, being a marked depressant to the heart muscle and also somewhat relaxant in its effects upon the arterioles. Moreover, Malherbe and Roubinovitch have proven with Rotain's sphygmomanometer that in man the arterial tension is almost always clearly lessened.

In 1902, Lotheisen reckoned the mortality from ethyl chloride as 1 in 16,000. McCardie collected 9700 cases in England, with 4 deaths. It would appear, therefore, that ethyl chloride is about as dangerous as an anesthetic as chloroform.

For prolonged operations the extreme fugaciousness of its action makes it less desirable than ether and chloroform; and for short operations nitrous oxide is so infinitely safer that the use of ethyl chloride as a general anesthetic seems hardly justifiable.

ETHYL BROMIDE is a colorless, very volatile, mobile liquid, having the specific gravity 1.49, of a sweet, chloroform-like smell; not readily inflammable. Any preparation of it which has color, or seems irritating, or has a disagreeable smell, is unfit for medicinal use. It must clearly be separated by the practitioner from *ethylene bromide*, which has a specific gravity 2.16, and solidifies at 32° F. into a crystalline mass. Scherbatscheff has collected four deaths produced by the substitution of ethylene bromide for ethyl bromide. Ethyl bromide degenerates under the influence of light and air, and should, therefore, always be kept in small bottles of dark glass, closely corked.

Proposed as an anesthetic in 1849, exploited by Rabuteau in France and by L. Turnbull in the United States in 1876-77, ethyl bromide has been used to a considerable extent as an anesthetic on account of the rapidity of its effects. It has, however, in recent years been almost totally abandoned in favor of ethyl chloride. Its influence usually manifests itself in a few seconds and lasts not longer than three minutes after the removal of the inhaler.

The physiological action of ethyl bromide has been partially studied by Schneider, Thornton and Maxwell, Abonyi, H. C. Wood, Ginsburg, and S. W. Cole with results apparently not altogether concordant.\*

All observers agree that in the narcosis the arterial pressure finally falls, but Ginsburg and Schneider note that this fall is preceded by a rise in the arterial pressure, which appears not to have been present in the experiments of Thornton and Maxwell or of H. C. Wood. The recent work of Tcherbacheff, who found that ethyl bromide causes death from cardiac paralysis with or without pulmonary oedema,

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\* We are not aware that the purity of the ethyl bromide used has been proved by any of the experimenters. Linguistic difficulties in regard to the Slavonic papers have compelled us to rely upon abstracts.

accords with the early conclusions of H. C. Wood—that ethyl bromide acts upon the heart in a manner similar to chloroform.

The respiratory action of ethyl bromide has not been carefully studied. It probably is a centric depressant. Livon finds, from analysis of the gases of the blood, that during the anesthesia produced by the ethyl bromide there is lessening of the carbonic acid with augmentation of the oxygen. According to Brinton it differs essentially from the other anesthetics in that there is no muscular relaxation during the narcosis.

In the absence of conclusive statistics, ethyl bromide appears to be at least as immediately dangerous as chloroform, and distinctly more so in its secondary results. It is true that Gilles claims that with a commercially pure bromide twenty thousand successive administrations of ethyl bromide in Germany had been without death, and that the fatal results have been due to impurity in the drug. This certainly does not apply to the deaths recorded by A. Gleich and Suarez de Mendoza.

**PENTAL—TRIMETHYLETHYLENE.**—This is a colorless, highly inflammable liquid, boiling at 100° F., originally proposed by W. Lombardino as a practical anesthetic. It acts with great promptness without marked disagreeable symptoms, producing a short narcosis, which is, however, longer than that caused by ethyl bromide. In three hundred narcoses by it, P. Philipp failed to find any depression of the heart or severe asphyxia. Pental is also commended by Kleindienst, who, however, noted that very frequently three or four days after the narcosis there was abundant albuminuria, and not rarely hematuria or hemoglobinuria occurs. In a study of the drug by David Cerna, anesthesia caused by it in the dog was found to be accompanied always by marked fall of the arterial pressure, and the conclusion was reached that the remedy depresses the heart. The alleged action of pental upon the kidneys, if it be true, negatives its use as a practical anesthetic. From the statistics of Gurlt, it is the most dangerous of all the anesthetics, there having been three deaths in the six hundred reported narcoses.

## PRACTICAL ANESTHESIA.

**Choice of Anesthetic.**—Although various substances have from time to time been used as anesthetics,\* the surgical profession has practically settled down to the employment of either ether or chloroform, and experience seems to show that there are no other known agents which act as well as do these two liquids. The question as to which of them should be preferred is a vital one, as are also the questions how to recognize and how to treat the accidents which occur during anesthesia. It must be, in the beginning, granted that the production of anesthesia is always attended by a danger which, though small, is positive, and that fatal accidents will always occur from time to time. There are few things in medical literature more tiresome than the arrogant assertions of various surgeons that they have never had a fatal accident from chloroform or ether because of

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\* From time to time various surgeons have essayed to assist in the production and prolongation of anesthesia by the use of narcotic alkaloids. Hypodermic injections of morphine given half an hour before the inhalation of the drug have been much employed, but it is doubtful whether they are of real advantage. In 1900, Schneiderlin proposed the substitution of *scopolamine-morphine narcosis* for ordinary surgical anesthesia and his method has found some following (see p. 111).



the special methods by which they have used them. May their conceit die with them. All that a surgeon can hope for is to reduce the number of these accidents to a minimum.

Chloroform has the advantages over ether,—that it produces anesthesia much more quickly, that it is less unpleasant to the patient, usually does not cause so much struggling and is less likely to be followed by after-nausea and vomiting. These advantages, while not to be lightly thrust aside, are not to be compared in importance with the question of the comparative danger of the two anesthetics. We may reach a conclusion as to this factor either by studying the statistics, or by a study of the physiological action of the two drugs.

For reasons given by H. C. Wood, in his address before the Berlin International Congress, it is doubtful whether one-half of the deaths produced by anesthetics have been reported, though many have been recorded. The consensus of the studies of Coates, Gould, Garree, and Gurlt, covering in all several millions of inhalations, places the mortality from chloroform at about one death in about 3,500 cases; from ether, at about one in 15,000. It must be considered established, therefore, that the ratio of deaths from chloroform\* is about four times greater than from ether.

The study of the physiological effects of the drug must likewise lead to the conviction that chloroform is much more dangerous than ether. Chloroform is, at least, as active a respiratory poison as ether and, besides, is a direct depressant to the heart, while the effects of ether upon that organ are comparatively slight. This opinion has been controverted by some, especially by the so-called Hyderabad Commission, but it seems unnecessary to-day to go into the details of the proof of this truth. The evidence brought out by H. C. Wood shows that—"chloroform acts much more promptly and much more powerfully than does ether, both upon the respiratory centres and the heart; that the action of chloroform is much more persistent and permanent than is that of ether; that chloroform is capable of causing death either by primarily arresting the respiration or by primarily stopping the heart, but that commonly both respiratory and cardiac functions are abolished at or about the same time; that ether usually acts very much more powerfully upon the respiration than upon the circulation, but that occasionally, and especially when the heart is feeble, ether is capable of acting as a cardiac paralyzant and may produce death by cardiac arrest at a time when the respirations are fully maintained." These conclusions have been confirmed by John A. MacWilliam, who has recorded cases of death in the lower animals from chloroform, in which there was primary collapse of the heart; and by the studies of the Lancet Commission, which found that out of three hundred and fifty-seven deaths caused by chloroform, whose

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\* It is probable that chloroform is less dangerous in tropical than in temperate climates. Evans presents evidence in confirmation of this to show that deaths from chloroform are more frequent during the cold seasons of the year. It is entirely possible that the increased volatility of this drug, at higher temperatures, facilitates its elimination from the body and therefore lessens the dangers of its use.



records it had examined, the fatal result was caused by cardiac failure two hundred and twenty-seven times, by respiratory failure eighty times, and by simultaneous failure of the two functions seventy-seven times.

On account of its danger we are firmly convinced that, under ordinary circumstances, ether should always be given the preference over chloroform in the production of general anesthesia. There are certain conditions, however, in which a careful surgeon is justified in his choice of chloroform.

Because of its far greater potency in proportion to bulk, in cases where the anesthetic has to be transported, as in military surgery, the impracticability of carrying the large quantities of ether necessary, affords justification for the use of chloroform. Further, in cases where rapidity of action is essential, as in strychnine-poisoning or under certain exigencies in military surgery, chloroform is again to be employed.

Besides these conditions, however, there are certain diseases which greatly enhance the danger of ether, and may properly lead to a preference of chloroform. Foremost among these stand inflammations of the respiratory tract. On account of the concentration of ether vapors, necessary to produce anesthesia, there is generally much more irritation of the respiratory mucous membranes, which may give rise to a dangerous or even fatal pulmonary inflammation.\*

Disease of the kidneys is frequently spoken of as an indication for a preference of chloroform. This opinion, however, is not well borne out by either scientific considerations nor yet by the practical results which have followed the use of the anesthetics.

Albuminuria may be considered a sufficiently accurate evidence of renal irritation to enable the practitioner to use it as a working test. A large number of studies as to the effect of anesthetics upon the urine have been made by different clinicians. Eisendrath states that albuminuria was produced in his cases,—25 per cent. by ether, 32 per cent. by chloroform; and casts were found in 28.3 per cent. after ether, 21.4 per cent. after chloroform. In Wunderlich's studies the results were 24.6 per cent. after ether, 34.8 per cent. after chloroform.† Ogden found tube-casts in 70 per cent. of etherizations. Statements of other investigators, whom we shall

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\* *Ether Pneumonia*.—Severe and even fatal pneumonia has so frequently followed the use of anesthetics that the possibility of its occurrence must be considered one of the serious dangers of anesthesia. Allowing that particles of food may enter the lungs during the narcosis and produce inflammatory changes, there has been a tendency to believe that ether pneumonia more frequently follows the use of ether than of chloroform, and is due to the local irritant action of the ether. The research of Richard Holscher has led him to the conclusion that the pneumonia is really due to the inhalation of bacteria from the mouth into the lung, that during etherization there is practically no irritation of the bronchial mucous membranes by ether, and that the râles which are heard during the narcosis are due to the inhalation of saliva which may largely be avoided by lowering the head, turning it to one side, and keeping the mouth as free as possible from the secretion. Any mechanical obstacle to breathing, according to Holscher greatly increases the likelihood of the inspiration of saliva, and the consequent danger of pneumonia. According to our belief, this research, although extremely important and suggestive as pointing out one cause of ether pneumonia, does not disprove the deleterious effect of the irritant action of ether.

† For elaborate articles on the action of chloroform on the urine and kidneys, see F. Nachod (*Archiv f. Klin. Chirurgie*, 1890, li.), also Offergeld. Babacci and Bebi (*Il Polyclinico*, 1896, iii.) reach the conclusion that, although ether produces slight changes in the kidneys more frequently than does chloroform, it never causes such profound alteration.

As bearing upon the question of the effect of ether anesthesia upon the kidney, it is interesting to state that F. S. Watson and W. T. Bailey have found that in the normal kidney, so far as the so-called Phloridzin Test is concerned, ether increases functional activity of the kidney, but when the kidney is already diseased seems from the beginning to depress the renal function (*Med. and Surg. Rep.*, Boston City Hospital, 1902).

not quote in detail, indicate that the occurrence of distinct albuminuria after anesthesia in persons with sound kidneys is less frequent than these statistics would indicate; but all the statistics strongly point towards the opinion that, while both ether and chloroform seriously affect the kidneys, ether is less dangerous than is chloroform. These clinical conclusions are certainly borne out by the results obtained in animals by various investigators. According to Kemp and Thompson, during etherization in the animal there is always accompanying the first rise of blood-pressure an expansion of the kidney followed by a shrinkage of the organ, if the anesthesia be prolonged; but this has been found by Buxton and Levy not to be a constant phenomenon. Buxton and Levy failed to produce complete suppression with ether, but did get lessening of the secretion and as the result of their research think that there is very little evidence to show that ether has an active, direct influence upon the secreting structure of the kidney. All observers seem to find that in chloroformization the volume and activity of the kidney steadily decrease.

The choice of the surgeon between the two great anesthetics should, in most cases of renal disease, be influenced by the existence of secondary effects of the disease. If, for instance, in any case there were pronounced degeneration of the heart-muscles, the selection should fall upon ether. If there were any reason, on the other hand, to believe that there was in the case a tendency to serous exudation, the danger of the production of œdema of the lungs by ether through its local irritant action would be sufficient reason for the selection of chloroform. In doubtful cases of cardiac complication it might be good practice to commence the anesthesia with ether, and, when once its stimulating action was established, to continue the narcosis by the use of chloroform.

**Examination of the Patient.**—Before administering the anesthetic, careful examination should be made by the anesthetizer for the determination of any physical condition which would enhance the danger of the anesthesia. Among these conditions most commonly to be looked for are: Organic Brain Diseases, including Tumors; Atheromatous Conditions of the Blood-Vessels; Organic Affections of the Heart, of the Lungs, and of the Kidneys.

**Brain.**—Brain-tumors and other organic forms of cerebral disease are very serious contraindications to the use of anesthetics; even where there is no demonstrable brain-lesion, if there be reason strongly to suspect atheroma of the vessels, anesthesia should be induced with the greatest reluctance. In a number of cases apoplexy has resulted during or immediately after the anesthesia. Moreover, death has frequently abruptly occurred immediately after the sudden removal of a large cerebral tumor—the introduction of the finger between the lobes of the brain—or other procedure which affects the intracranial pressure. These deaths have resulted both from respiratory failure and from sudden cardiac arrest, and are probably the result of the loss of the resisting power of the respiratory and vaso-motor centres, making them unable to withstand variations of brain-pressure which in their normal condition would not seriously influence them. It is evident that the surgeon should be as careful as possible in his operative procedures to avoid sudden disturbances of the brain. Which anesthetic is to be given the choice, in diseases of the brain, there is

not yet sufficient evidence to clearly indicate. There has been in some, to a certain extent, a feeling, not supported by any positive evidence, that chloroform is preferable, but in a discussion which took place in the College of Physicians of Philadelphia, November, 1902, a number of cerebral surgeons of large experience were unanimous in asserting that, in cerebral surgery, ether is the least dangerous anesthetic.

*Heart.*—When valvular disease of the heart does not produce any distinct functional disarrangement of the heart, and when the heart-muscle is in a fair condition of health, anesthesia may be induced, provided the circumstances of the case are such as to justify the surgeon taking a slightly increased risk. The key to the situation is not the valvular lesion, but the condition of the muscle. A loud murmur usually depends for its loudness not only upon the character of the valvular lesion but also upon the force which drives the blood through the diseased orifice. A loud murmur is, therefore, on the whole, not more strongly contraindicative of anesthesia than is a feeble one; indeed, as the feeble murmur is more commonly associated with feeble heart-walls, greater care must be exercised when such murmur exists than when a loud bruit everywhere forces itself upon the physician's attention. In all cases of heart disease, whenever it is possible to avoid the use of an anesthetic by the employment of cocaine or by other local device, this should be done. No condition of the heart is, however, an absolute contraindication to the use of the anesthetic; under certain circumstances anesthesia may be produced when the heart is in advanced fatty degeneration. It must be remembered that the shock and nerve-strain which attend a major surgical operation without anesthesia would endanger the arrest of a fatty heart even to a greater degree than would the anesthesia, so that the question is, after all, as to the imperativeness of the proposed operation.

In diseases of the heart the action of chloroform upon the heart makes it very dangerous. In cases with wide-spread pulmonic engorgement, and a tendency to exudation into the lung-vessels and smaller bronchial tubes, the local irritant action of ether upon the mucous membranes is so deleterious that the surgeon is placed, as it were, between Scylla and Charybdis, and may in an individual case have great difficulty in deciding what is best. Some surgeons prefer under these circumstances the so-called *A. C. E. Mixture*, which contains too much chloroform to be of any advantage. A better mixture consists of six parts of ether and one of chloroform, added together at the time of use. Chloroform is especially dangerous when orthopnoea exists; it is doubtful whether in such a case its use is ever justifiable.

*Lungs.*—Organic disease of the lungs seems to be a less serious bar to the use of anesthetics than might naturally be expected. The danger appears to be in proportion to the acuteness of the disease rather than to its extent. A chronic pulmonary condition, such as



tuberculosis, may involve a considerable proportion of the pulmonary area without forbidding the use of the anesthetic, while in ordinary acute bronchitis the anesthesia may be attended with grave risk. Only under the most urgent circumstances should anesthesia be attempted when in an acute pulmonary disease the symptoms are of sufficient intensity to produce even slight dyspnœa. In recent pleurisy or pleuro-pneumonia, with any embarrassment of the respiration or duskiness of the countenance anesthetization is almost absolutely unwarrantable.

Of the chronic pulmonic affections, probably emphysema, associated as it so frequently is with weakness of the right heart, causes the most solicitude to the anesthetizer. The irritant local action of ether is an important element when the lining membrane of the tubes or air-vessels is seriously implicated; indeed, our own opinion is very positive that in some of the deaths which have occurred in persons with diseased kidneys from œdema of the lungs directly after etherization the cause of death has been the local irritant action of the ether. It would appear also that wide-spread organic changes in the lungs sometimes so interfere with the absorption of ether that it becomes exceedingly difficult to produce complete anesthesia. The dictum of Hewitt, that in extreme emphysema, in chronic bronchitis attended by expectoration and dyspnœa, and in advanced pulmonary phthisis, chloroform or some other mixture containing chloroform should be employed, is, we believe, correct.

In obstructive laryngeal disease, or when contraction of the lumen of the trachea, either from within or without, produces dyspnœa, extreme caution must be exercised in the use of the anesthetic. Under these circumstances the chances of ether increasing the mechanical asphyxia by irritating the larynx or trachea are very great, so that chloroform is preferable; or chloroform may be employed at first, and ether given when the reflexes have been abolished by the obtunding of the nerve-centres. When the laryngeal obstruction is of the nature of a spasm and not of an organic change, the use of the anesthetic is free from extraordinary danger; but it must be remembered that frequently in such cases there is more or less laryngeal irritation, so that chloroform is preferable to ether,—a conclusion which is strengthened by the necessity which often exists for the prompt action of the anesthetic.

In certain cases the mechanical obstruction may be a tumor in the mouth or other lesion above the respiratory tract proper, but if the respiration be interfered with, the general principles just enunciated hold good.

*Hepatic Conditions.*—L. G. Guthrie has called attention to the excessive fatality attending the use of chloroform in children suffering from fatty degeneration of the liver. The time of death in nine recorded cases was from ten hours to nine days after the operation, so that the cases really belong among those considered in the After-effects of Anesthesia (see page 49). There is sufficient ground for the generali-



zation that anesthesia should be produced with the greatest reluctance in all persons suffering from chronic fatty degeneration of the liver, and that when anesthesia must be produced in such cases, ether and not chloroform should always be selected.

*Diseases of the Kidney.*—So far as our reading goes, Thomas A. Emmet was the first to report cases of fatal urinary suppression produced by the inhalation of ether in persons suffering from chronic Bright's disease. His statements have been followed by reports of numerous similar cases, and led to the wide-spread opinion that ether should not be used when there was chronic disease of the kidneys. It is now, however, established that chloroform is capable of causing severe renal irritation, and the whole drift of the evidence is to show that in this respect it is much more active than is ether, so that, though renal disease is a contraindication to the use of any anesthetic, if anesthesia must be produced under the circumstances, ether is safer than is chloroform. (See p. 39.)

In regard to the preparation of the patient aside from his physical examination, the rules are very simple, but very important.

First, except in emergency operations, the anesthetic should not be given less than six hours after a meal; second, clothing should always be loose, so as to not obstruct in any way respiratory movements; third, false-teeth, and other movable objects should be taken out of the mouth; finally, the anesthesia should always be commenced in a recumbent posture.

**Administration of the Anesthetic.**—The question of the inhaler to be used is one of some importance. Although not able to give definite statistics upon the fact, we are strongly inclined to believe that deaths from anesthesia, and especially from ether, are proportionately more frequent in Europe than in America. If this be so, one reason, it seems to us, is to be looked for in the use of the Clover and other forms of closed inhalers, with which the anesthesia produced is to a greater or less extent due to mechanical asphyxiation. Sherrington and Sowton have shown that the presence of carbonic acid in the perfusing liquid, exaggerates the depressant action of chloroform upon the heart.

For the inhalation of ether the inhaler invented by O. H. Allis is probably as good as any upon the market. It is based upon the theory that the patient to be etherized should be supplied with an abundance of air impregnated with the vapor of ether. It consists essentially of a series of foldings of muslin on a wire framework, arranged almost like the gills of a fish, so as to allow the air to pass

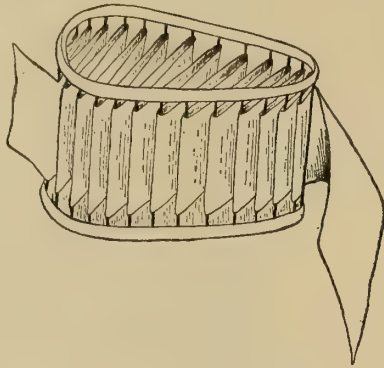


FIG. 2.—ALLIS ETHER INHALER.

freely through, but everywhere to come in contact with the ether. The ether is dropped or sprinkled equally over the whole surface of the muslin, whence it is rapidly evaporated so that the patient can receive as large a dose as desirable of the anesthetic yet the respiration be not in the least interfered with. For chloroform, preference may be given to Esmarch's inhaler or one of its various modifications. This consists of a light wire framework over which is fastened surgical gauze, the framework being so arranged that the gauze is held some distance from the patient, avoiding the danger of inhaling the concentrated chloroform vapors. An inhaler which has received considerable commendation in Europe is the Roth-Dräger inhaler, an apparatus invented for the purpose of giving a mixture of chloroform with oxygen. It is claimed by Roth that under these circumstances the chloroform remains unchanged, although Ernst Falk believed that his chemical studies have demonstrated that after twenty minutes of narcosis there is a distinct decomposition of the chloroform. Either ether or chloroform, however, may be safely and confidently administered without the use of any more complicated mechanism than a few thicknesses of surgical gauze. Four or five thicknesses of gauze may be lightly held over the mouth and nose of the patient and the ether dropped, drop by drop, upon the gauze just below the nostrils. When chloroform is the anesthetic the gauze should be held a little distance from the face to allow the admixture of air beneath the gauze.

The unpleasant sensation which gives the patient so much discomfort may be largely avoided if not altogether obviated by a very slow administration, beginning with one or two drops at a time and increasing gradually as the patient becomes accustomed to the anesthetic until the appearance of delirium of the first stage, when, if ether is being used, it should be pushed as rapidly as possible. It must be remembered that the danger from ether is largely proportionate to the total quantity of the anesthetic, while the danger from chloroform is chiefly dependent upon the concentration of the chloroform vapor in the air at a given moment. Never more than three and one-half per cent. of the chloroform should be contained in the inspired air.\*

The use of ether at night requires care. We have seen a flame, by lighting the vapor, pass over eight feet and set on fire the ether sponge and the patient. Since the vapor of ether is heavier than air, when the anesthetic is used at night the light should always be elevated. The administration of chloroform at night is also not free from danger. Attention has been called by various practitioners to violent catarrhal inflammations of the respiratory passages, and even to fatal pneumonias, which have been produced by the use of chloroform in confined rooms with artificial light. It has been shown by the analyses of Bosshard and others that, under the circumstances mentioned, by

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\* For methods of determining the percentage of chloroform in a mixture of its vapor with air, see *Brit. Med. Journ.*, 1903, vol. i. p. 1420.

the decomposition of chloroform there is liberated free chlorine and also phosgene gas, to which probably are due the local inflammations.\*

**Symptoms.**—The narcosis produced by ether and chloroform may be, for convenience, divided into three stages: First, excitement; second, anesthesia; third, collapse.

The first stage is usually more marked with ether than with chloroform. The first symptoms observed are a sense of choking which is referable to the irritant action of the vapor upon the mucous membranes of the upper respiratory tract. This irritation of the fauces may lead to great irregularity or even to complete cessation of the respiration.

The respiratory phenomena seem to be the same in the lower mammalia as in man. The primary arrest of respiration during the first stages of etherization is undoubtedly due to a local irritation of the mucous membranes of the air-passages. According to Kratschmer, in the rabbit it is prevented by previous section of the trigeminal nerves, but not by division of the vagi; nor does it occur when the ether is administered through a tracheal fistula. This would indicate that the respiratory disturbance is due to irritation of the peripheral trigeminal nerves, but H. A. Hare has found that in the dog tracheal irritation with ether produces respiratory arrest, which is, however, prevented by previous section of the vagus. As stated by P. Knoll, the arrest of respiration is sometimes replaced by very irregular breathing. The importance of the matter is increased by the fact that Kratschmer has noticed that the disturbances of respiration are accompanied by spasm of the glottis. It is evident that these disturbances are reflexes due to irritation of the trigeminal nerves in the upper, and of the pneumogastric filaments in the lower respiratory tract. They are especially interesting in connection with the asserted direct or indirect effect of ether upon the recurrent laryngeal nerve.

Partly as a result of the irritation of the respiratory tract, but largely on account of the alcohol-like delirium produced, the patient struggles more or less violently. As in alcohol, the delirium of ether or chloroform is of various characters; some patients weep, others laugh; some shout, some pray, some rave, and some become exceedingly pugnacious. In rare instances the dreams are erotic; and cases are on record in which there were distinct evidences of the occurrence of a complete venereal orgasm. In this stage the patient in most cases may be more or less perfectly aroused. In rare instances however, unconsciousness has been retained until complete anesthesia.† The face is warm, flushed and moist. The pulse is somewhat more rapid than normal, largely on account of the struggling of the patient, but of good volume. The pupil may be somewhat dilated but readily contracts to light.

The second stage is that of surgical anesthesia. There is complete loss of sensation with unconsciousness, the patient being in a deep stupor from which he cannot be aroused. The reflexes are mostly abolished although certain ones, the conjunctival and respiratory reflexes, may be retained. The muscles are relaxed but keep their

\* Consult Zweifel (*Berl. Klin. Wochenschr.*, 1889), D. R. Patterson (*London Practitioner*, xlii.), and Brandenburg (*Corr. Bl. f. Schweizer Aerzte*, 1897, xxvii.; *Arch. f. Hygiene*, 1891, xiii.).

† Coleman (Sansom, *Chloroform*, Philadelphia, 1866) states, that he has extracted his own teeth without pain; and Snow relates the anecdote of a child who played with his toys during the operation of lithotomy.



normal tone. The pulse is, with ether, usually somewhat more rapid than normal and of good volume; when chloroform is the anesthetic, it is often much softer than normal. The respirations are slow but regular and deep. The face is flushed, the skin is warm and moist. The pupil is generally contracted.\*

In the third stage there is profound collapse, with rapid feeble pulse, very infrequent and shallow respirations. The face is of a peculiar livid pallor the result of combined circulatory and respiratory failure. The pupil is dilated and non-irritable. All the reflexes are entirely abolished and the muscles lose their tonicity. As a result of this loss of muscle tone we get the stertorous respiration and drooping of the corners of the mouth.

**Accidents.**—In practical anesthesia it is a matter of the gravest importance to recognize the coming on of accidents. The danger signals to be looked for are: Dilatation of the pupils, the very slow or irregular respirations, stertorous breathing, extreme rapidity or feebleness of the pulse, changes in the color or expression of the face.

Before epitomizing the treatment of the accidents of anesthesia it seems proper to discuss in detail certain mechanical measures which may be practised with advantage,—namely, Inversion of the Body, Cardiac Massage, and Artificial Respiration.

*Inversion of the Body.*—In the first edition of the present treatise it was written: "Whenever there is any failure of the heart's action, as is nearly always the case, the body should be laid at an angle of forty degrees, with the head downward, so as to favor the passage of arterialized blood to the brain" (E. L. Holmes). Some years after this the method was asserted in France to have just then originated with Nélaton. It undoubtedly has value. The body of the animal whose circulation has been paralyzed by chloroform acts in a measure like a tube filled with liquid. When the feet are raised above the head there is a marked increase in the blood-pressure in the carotid, with decrease in the blood-pressure in the femorals; and when, on the other hand, the feet are dropped below the head, the blood-pressure falls in the carotid, but rises in the femorals. The respiration is not affected by the procedure, but a heart which has entirely ceased will often suddenly resume its work when the feet are elevated. Inversion causes the blood which has collected in the extremely relaxed abdominal vessels to flow into and distend the right side of the heart, and this distention may have sufficient influence to stimulate into action a failing organ.

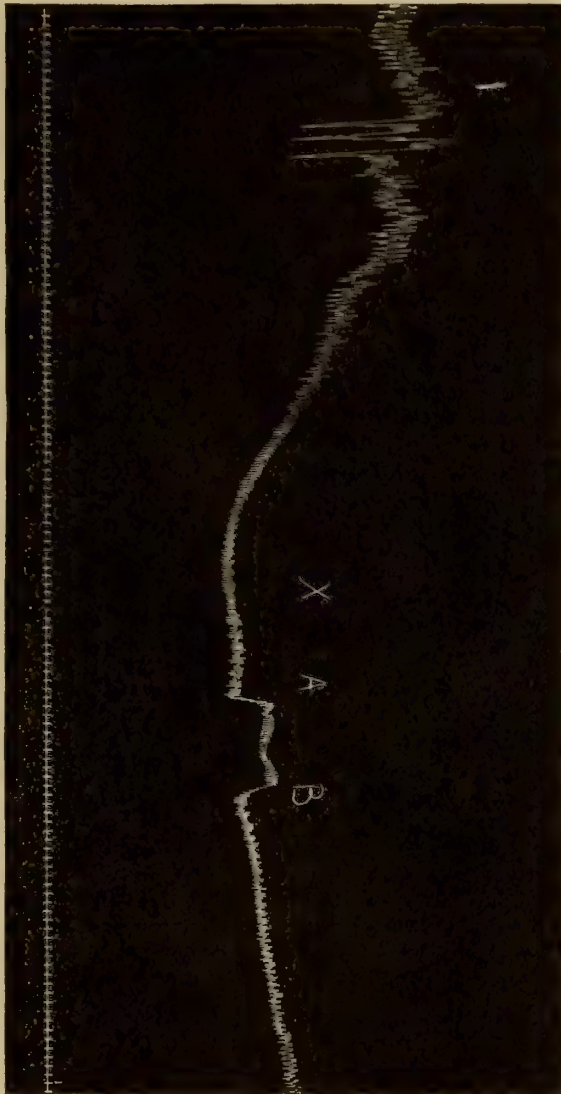
*Cardiac Massage.*—In 1889 Prus succeeded in restoring animals to life, after cardiac arrest during anesthesia, by rhythmically contracting the bared heart with his fingers, and this so-called "cardiac massage" has been employed to a considerable extent by surgeons. W. W. Keen collected twenty-eight recorded cases with four successes; since this paper one complete recovery has been reported by Sen-

\* Baudin (*Le Progres Méd.*, Sept. 1874) called attention to the pupil as a guide in chloroformization, stating that, although at first it is uniformly dilated, afterwards it is uniformly immovably contracted, and that this is the period for operating. Schläger is in accord with Baudin; in one hundred and twenty out of one hundred and twenty-two cases observed, the pupil was dilated during the stage of excitement, and during complete anesthesia narrowly contracted. He also states that if during anesthesia the pupil return to normal, more chloroform is required, but if it suddenly dilate, danger is imminent. At present, however, the condition of the pupil cannot be considered a safe guide in anesthetization. Dogiel (*Reichert's Archiv für Anat.*, 1866) affirms that in rabbits, during the stage of excitement, the pupil is contracted, during anesthesia dilated. Schiff has strenuously combated the conclusions of Baudin; and in a very careful series of experiments on animals W. H. Winslow found that the state of the pupil varies greatly in the same stage of anesthesia. Thus in complete anesthesia, sometimes the pupil was widely dilated, sometimes contracted; and death sometimes occurred with a dilated, sometimes with a contracted pupil,—in the former case probably being syncope, in the latter asphyxial (*Phila. Med. Times*, vi. 275).



cert. Three methods have been used: (1) By compression between the hands, one being applied outside the chest and the other directly upon the heart after an abdominal section, but without opening the diaphragm. (2) By abdominal section, and after opening the diaphragm seizing the heart within the pericardial sac. (3)

FIG. 3.—SHOWING THE EFFECT OF ELEVATING THE FEET DURING CHLOROFORM NARCOSIS. X—Withdraw chloroform. A to B—Feet raised above head. Time marker indicates 2 seconds.



By resection of the chest wall, incision of the pericardium, and grasping the heart with one or both hands. The third of these methods involves a major operation in surgery, adding distinctly to the surgical dangers of the patient. Especially when the abdomen has already been opened by the surgeon, the first, and even the second method is easily practised without very serious surgical results. It is at present doubtful whether cardiac massage will ever restore cardiac action when the intra-

venous injection of adrenalin and the practice of forced artificial respiration would not succeed, but to the use of these methods that of the simpler form of cardiac massage (No. 1), especially in abdominal operations, may well be added.

*Artificial Respiration.*—The one measure which we have found in experiments upon fatally anesthetized animals to surpass, in practical efficiency, all others combined is artificial respiration, by means of which animals may be frequently resuscitated *after all cardiac and respiratory movements have apparently ceased.*

It is evident that the ordinary methods of practising artificial respiration in man are exceedingly imperfect and feeble, and that in the accidents of anesthesia so-called *forced artificial respiration* should be at once employed. The principle of forced artificial respiration consists simply of pumping air into the lungs by means of a bellows. There are several forms of apparatus for this purpose to be had, nearly all based upon the principle originally brought forward by Fell.

In using this apparatus, the lungs should be thoroughly but slowly expanded by each stroke of the bellows, and a respiratory rate of about sixteen to twenty a minute be steadily maintained. It is essential to free the lungs and blood of chloroform as rapidly as possible, by quickly changing the residual air of the lungs; but of course due care must be exercised that no force sufficient to rupture air-vesicles be employed. When the symptoms are protracted, and the bodily temperature falls, the bodily heat must be maintained by external warmth, and the temperature of the room, unless the air entering the lungs be artificially heated, should not be less than 80° F.

When no apparatus is at hand mouth to mouth insufflation may be tried. A. E. Prince reports a case saved in this way.

In the light of all our present clinical and experimental knowledge, the following rules may be formulated as embodying the treatment of the accidents of anesthesia:

*First.*—Unless the pulse be beating actively, partially or wholly invert the body of the patient.

*Second.*—Place the index fingers of each hand upon the corresponding cornua of the hyoid bone, while the middle fingers rest upon the angle of the jaw, and then press forward and upward, the same force serving to extend the head upon the neck; if this fail to open the glottis, by means of a tenaculum, thrust far back into the base of the tongue, draw it forward.

*Third.*—Make a momentary effort to stimulate respiration by slapping the chest, by douching with cold water, or by the method, suggested by Hare, of pouring a little ether on the bared abdomen, so as to get the effect of cold. Do not waste time, if respiration has failed, in any of these attempts.

*Fourth.*—Certain drugs are of great use. For stimulation of the respiration strychnine is the most potent agent we have; cocaine is useful as an adjunct. For failing circulation digitalis would be a most valuable remedy were it not so slow in its action; it should, however, be given hypodermically, in the hope that it may act in time to be of benefit; probably injected intravenously it would be a very valuable remedy, but we know of no clinical records of such use. Adrenalin given intravenously is a very quick and powerful circulatory stimulant but should not be used indiscriminately on account of the danger of causing pulmonary oedema (see p. 246). In severe cases of cardiac failure, however, it is of the utmost service. It

should be administered intravenously in hot (105° F.) normal saline solution;\* from twenty to thirty minims of the 1 : 1000 adrenalin solution in half a pint of the saline solution may be slowly injected, as much as two drachms of the adrenalin solution in two pints of the normal saline may be given in the course of one and a half hours. Avoid the use of alcohol, it is capable only of harm. The same is probably true of nitroglycerin.

Owing to the closeness of the relations of alcohol to ether and chloroform, H. C. Wood many years ago taught that the administration of alcohol during anesthesia was a doubtful procedure; subsequently, R. Dubois determined that in the alcoholized animal much less chloroform is required to kill than in the normal animal. Then H. C. Wood experimentally proved that alcohol injected into the vein of a dog whose heart is depressed by chloroform, if in sufficient dose to exert any perceptible influence, always increases the cardiac weakness, or, if in considerable dose, immediately paralyzes the viscus. Without doubt patients have been killed by alcohol given to relieve cardiac failure during anesthesia. Experiments similar to those with alcohol just spoken of were made by H. C. Wood: with ammonia, which was found usually to have a distinct, although very fugacious, influence upon the chloroformed heart; with digitalis, which was found to have a very powerful stimulant influence upon the heart and blood-pressure; with amyl nitrite, which failed to produce any pronounced influence for good; with caffeine, which seemed to have little or no power; and with strychnine, which had some slight influence upon the blood-pressure, but an enormous one upon the respiration of the chloroformed animal. Thus, a respiration which had practically ceased for ten seconds, suddenly, under the influence of an injection of strychnine, became very quick and full. Cocaine was not tried, but studies since made with it upon chloralized dogs indicate that it has distinct value, especially when given with the strychnine. At the time of the experiments just spoken of adrenalin had not been discovered, but as the most powerful known stimulant to the circulation it must be of great possible value in the treatment of the cardiac accidents of anesthesia.

*Fifth.*—Maintain the temperature of the body by the external application of heat.

In 1848 Duméril and Demarquay showed that during anesthesia there is a reduction of temperature. This has been confirmed by Bouisson and by Sulzynski. This fall of temperature may, when narcosis is prolonged, amount to 2° F. Whether this fall of temperature be, as asserted by Scheinson, due to a lessened production of the bodily heat, or whether, as seems to us more probable, it be the outcome of an increased dissipation of bodily heat, is of no practical importance to the surgeon. The immediate lesson is, that prolonged severe operations should be done in very hot rooms, and that when the bodily heat falls it should be maintained by the external use of heat, in some cases even by the employment of a hot-water mattress.

*Sixth.*—Practise artificial respiration immediately and very actively throughout (forced respiration if the apparatus be at hand), even when the heart is primarily affected. It must be remembered that the residual air of the lung may retain the vapor of the anesthetic and continue to yield it to the system for a considerable time after the cessation of its administration.

**After-Effects of Anesthesia.**—Many years ago Liman affirmed that at least some of the deaths following operations which have been

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\*The restorative cardiac action of hot normal salt solution intravenously administered has been demonstrated in a series of experiments upon animals by S. Gomberg.



attributed to the operative procedure have been due to the chloroform. The correctness of this view we have demonstrated by having such deaths occur in the lower animals after both chloroform and ether when there had been no surgical operation, the animal regaining consciousness, but by and by passing into a condition of profound asthenia, with loss of all functional power, ending in death. These deaths are due to anatomical changes in important organs.

About a decade since it was shown by Unger and by Path, that when, in the dog, narcosis is maintained for a length of time by the inhalation of chloroform, there is produced a fatty degeneration which is usually most marked in the liver and kidneys and in the heart-muscles, but may be pronounced in the spleen, in the general epithelial tissues, and in the voluntary muscles. These researches have been confirmed in their general results in numerous experiments upon animals by Strassmann, by Ostertag, and by Kast and Mester. Tedeschi, in an elaborate study upon guinea-pigs, has found that the first anatomical alteration produced by chloroform consists of cloudy swelling which may go on to degeneration, or may subside; and that even when a considerable degree of apparent fatty degeneration has occurred recovery is possible. He also found that these alterations were most severe in the nervous system, which is somewhat contrary to the general opinion. Botscharoff and S. Schmidt assert that they have demonstrated alteration of the heart-ganglia, especially vacuolation of the cells, after prolonged chloroformization.

Eugene Fraenkel found in four human subjects, dying after prolonged chloroformization, wide-spread necrotic degeneration, especially affecting the heart-muscles and the epithelium of the kidney, and Carmichael and Beattie, and Stiles and Macdonald have reported wide-spread fatty changes in man following chloroform anesthesia. As these observations have been abundantly confirmed (Bandler, Ambrosius, and our own laboratory), it must be considered proved that chloroform has the power of producing tissue-degeneration, ending in death.

The possibility of after-effects from the anesthetic should certainly influence the choice of surgeons.

According to Desgrez and Nicloux, chloroformization of the lower animals causes a great increase in the amount of carbon monoxide in the blood. As this substance is produced by the decomposition of chloroform by an alkali, and as Desgrez and Nicloux have failed to find that it is increased in the blood by etherization, it probably is produced in the blood by the destruction of the chloroform, which destruction must be accompanied by the formation of various chlorine compounds.

On the other hand, the destruction of ether in the system can scarcely yield other than harmless educts, so that, *a priori*, after-effects are much more probable from the use of chloroform than from ether. This probability is strongly confirmed both by experimental and clinical evidence. As the result of many years' experience in the physiological laboratory, we are very sure that after-deaths are much more frequent in animals which have been chloroformed than after ether.

In experiments performed by William Carter and H. C. Wood in the University of Pennsylvania changes similar to those caused by chloroform were found in the dog after etherization. These studies have been corroborated by the researches of Ferdinand Schenck and of Tedeschi. Again, in a woman whose death occurred twenty-four hours after a prolonged etherization in the University Hospital, without obvious cause, wide-spread tissue-changes were found. Müller found that chloroform, ether, ethyl chloride, ethyl bromide, and hydrated chloral were all capable of producing these changes, but that they were less marked after ether than after chloroform. In his experiments it was found that if a second narcosis was produced before the repair processes were completed the baneful effects were much intensified even if different anesthetics were used. He warns therefore that after a prolonged anesthesia no second narcosis should be undertaken for at least three days.

In this connection may be mentioned the observations of E. Becker who, in two hundred and fifty experiments made with ether, ethyl bromide, and chloro-



form, found that the anesthesia was followed by pronounced acetonuria, which he believed to be due to increased destruction of albumin. In three diabetics he noticed great increase in the amount of acetone in the urine,—an indication that under certain circumstances diabetes should be considered a contraindication to the use of an anesthetic. Brachett, Stone and Low report seven cases of fatal acetonuria following ether anesthesia in children suffering with muscular atrophies.

### LOCAL ANESTHESIA.

Of the drugs which are employed for the production of local anesthesia, cocaine still stands pre-eminent, but its common use for other purposes has led us to discuss its physiological action and therapeutic use fully in the chapter on Delirifacients see p. 117).

**EUCAINE.**—Under the name of eucaine two allied chemical substances have been put upon the market, each depending, according to Vinci, for its anesthetic properties upon the presence of a benzoyl molecule in its constitution. These substances have been distinguished in commerce by the names of Alpha-Eucaine and Beta-Eucaine. Alpha-Eucaine is chemically *n*-methyl-benzoyltetramethyl-y-oxy piperidincarboxylic methylester; Beta-Eucaine is benzoylvinyldiacetonalkamine. *Eucaine* of the drug stores is at present *beta-eucaine*. Beta-eucaine is soluble in water to the extent of about three and one-half per cent. The acetate has been proposed as more soluble.

According to Vinci, *alpha-eucaine* is a depressant to the spinal cord, and Ver Eecke has found it to be a direct muscle paralyzant which acts more powerfully upon the heart-muscle than upon the voluntary muscle, so that death from cardiac diastolic arrest occurs before complete general paralysis. Ver Eecke states that in mammals the arterial pressure is markedly affected and the respiration is first stimulated and finally paralyzed centrally. The same author failed to find the poison in the urine after its administration, and believes that it undergoes destruction in the body. He also states that in chronic poisoning with alpha-eucaine there is a wide-spread fatty degeneration which is especially marked in the heart-muscle.

Vinci found that *beta-eucaine* paralyzes the peripheral motor nerves as well as the sensory, does not dilate the pupil, paralyzes the vaso-motor centres, and slows the heart even after the vagus has been paralyzed with atropine.

As a local anesthetic eucaine is somewhat less powerful than cocaine, and does not produce primary vaso-motor constriction nor vaso-paralytic after-effects. The three- to five-per-cent. solution will rapidly and completely anesthetize the cornea without dilating the pupil or paralyzing the pupillary reflexes. It may be used in solutions of from 2 to 10 per cent.

The influence of eucaine upon the general system is so slight that fifteen grains of it have been injected hypodermically (G. W. Spencer) without the production of any marked symptoms. It may prove of value in gastric pain or vomiting. The maximum dose is said to be three grains (0.2 Gm.).

**TROPACOCAINE.**—This alkaloid was isolated by Giesel from the narrow-leaved coca-plant of Java. It is obtained as an oily liquid, which solidifies in radiating crystals, and is soluble in chloroform, ether, or petroleum benzin. It has been physiologically studied by Arthur P. Chadbourne, who finds that locally it acts in a manner similar to cocaine, without, however, causing ischemia or congestion of the mucous membrane with which it is brought in contact. It was found by Chadbourne to be only half as toxic as cocaine. In lower mammals it produces, in sufficient dose, loss of coördination, followed by violent convulsions, disturbances of the respiration, coma, and death by centric asphyxia. The convulsions are of cerebral origin. Upon the circulation the drug seems to have only a comparatively feeble influence, causing, however, when in sufficient amount, a steady fall in the arterial pressure. The temperature usually begins to rise before the convulsion, and has

been noted as high as 4° C. above the normal. When tropacocaine is put in the eye, anesthesia is said to come on and disappear more quickly than with cocaine, sensation being suspended in less than half a minute after the application of a three-per-cent. solution: mydriasis is usually absent, never very pronounced.

It is claimed for tropacocaine that it is especially superior to cocaine for the production of spinal anesthesia, being very much less likely to produce fever and other disagreeable symptoms (K. Schwarz and F. Neugebauer). According to Neugebauer, 0.05 to 0.06 grammes of the alkaloid may be injected.

ORTHOFORM is a white bulky powder very slightly soluble in water. It will not produce loss of sensation through the skin nor mucous membrane but is an efficient anesthetic when applied to raw surfaces. As it also possesses some antiseptic power it is used chiefly as a dusting powder to *burns* or other painful *wounds*. In *gastric ulcer* it will at times greatly relieve the pain, for which purpose five to ten grains (0.3–0.6 Gm.) may be given at a dose. It is of great service in alleviating pain in *tuberculous laryngitis*.

STOVAINE.—This benzoyl derivative was brought forward by Tourneau as being less toxic than cocaine. It has been used in spinal analgesia by Tuffier, who asserts that it is not followed by unpleasant after-symptoms. He injected one-half C.c. (8 minims) of a ten-per-cent. solution. It should not be used in connection with adrenalin.

**Practical Local Anesthesia.**—If it were possible to prevent the absorption of one of the active local anesthetics, after its injection into a tissue, for a sufficient length of time, the method of local anesthesia would be applicable to a very large proportion of surgical operations. When, as in the case of a felon, the part to be operated on can be tightly surrounded by a constricting bandage, so as to almost entirely shut off circulation, it is very easy to inject a local anesthetic and afterwards to operate without the production of pain. Rarely, however, is the surgical task so easy, and the several processes discussed below have been invented for the purpose of overcoming the practical difficulties.

*Infiltration-Anesthesia.*—In this process, as devised by Schleich, the original attempt was to increase the activity of cocaine by adding to its benumbing power the influence of the interference with the circulation of the part, and of pressure upon the nerve-trunks of the part, produced by the injection of large quantities of water directly into the tissue to be operated on. In this process, as originally devised, the skin having been frozen by means of an ethyl spray, the point of a large hypodermic syringe is thrust into its papillary layer and a small mass of the fluid is injected, not under, but into, the skin. The needle of the syringe is then pressed in a little deeper and a new injection made, the process being continued until a sufficient depth is reached. This method has been applied not only in minor but also in major surgery. During a large operation it may be necessary to repeat, from time to time, as the knife of the surgeon cuts more and more deeply into the tissues.

Three solutions were used by Schleich. No. 1, of medium strength, may be made by dissolving, at the time of using, a powder composed of one and a half grains of cocaine hydrochlorate, one-third of a grain of morphine hydrochlorate,

and three grains of common salt in twenty-seven drachms of sterilized water. No. 2, the weakest solution, contains only one-tenth the percentage of cocaine in No. 1; while No. 3, the strongest solution, contains double the percentage. No. 3 is used only when there is an active inflammatory lesion of moderate extent, as in case of a *furuncle*. In many cases it is essential that not only the part to be opened but the tissues beneath it be infiltrated. Thus, a furuncle or abscess may be completely encompassed with a zone of artificial oedema.

A most important modification of the method of Schleich's infiltration anesthesia has been brought to the notice of the profession by its inventor, H. Braun, who found that if, by local cooling, the vitality and circulation of a tissue be interfered with, absorption of the injected cocaine will be so long delayed that the symptoms of poisoning will be put off almost indefinitely or may fail to develop at all. Acting upon this knowledge, Braun obtained from the conjoint use of adrenalin and cocaine such satisfactory results as to apparently open a new field for the use of local anesthesia: by employing a one-to five-per-cent. solution of cocaine to which had been added from 1: 10,000 to 1: 100,000 of adrenalin, and beginning the operation from one to one and a half hours after the injection, he was enabled to do trunkal operations without causing suffering.

Braun's method for the production of local anesthesia has been followed by so much of success by various surgeons\* that it would seem to be demonstrated that adrenalin, by its powerful constricting influence upon the blood-vessels, not only very sensibly increases the benumbing action of the local anesthetic, but also, by lessening the rate of the absorption of the drug, greatly increases the duration of its local activity. The further suggestion of A. E. J. Barker, that the conjoint use of beta-eucaine and adrenalin affords a most excellent method of producing infiltration-anesthesia, has been followed out by various surgeons with great satisfaction.

In his original discussion of infiltration-anesthesia, Schleich recognized that it was possible to produce a transitory anesthesia by infiltration with pure water, and it has been shown by S. G. Gant that in cases of superficial abscesses and other surgical diseases, and in situations in which injected water will for the time being, as it were, be dammed up in the tissues, it is possible to do painless minor operations by simply throwing sterile water into the parts in such amounts as to produce great distention. The technique of the method is as follows: A fold of the skin on one end of the line of the incision is compressed between the thumb and forefinger, and then has slowly injected into it a few drops of water so as to produce a small, localized, blister-like distention. This is repeated until the whole line of incision has been gradually injected with water *into*, not *under*, the skin. The needle is plunged through this distended line, and subcutaneous injections are rapidly made until a firm, whitish, ridge-like swelling is produced, through which the incision can usually be made without pain.

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\* See Braun, *Cb. C.*, 1903; Honigman, *Ibid.*; Gangitans, *B. M. J.*, 1903, ii.; Lefmann, *M. M. W.*, 1902; Braun, *A. K. C.*, Bd. lxi.



The method seems to be especially applicable to rectal diseases. In external thrombotic *hemorrhoids* the water should be injected between the layers of the skin overlying the clot; in cutaneous hemorrhoids both the skin and the tumor should be distended tightly; in external hemorrhoids each tumor must be distended so tightly as to cause it to turn white. In rectal operations the skin and subcutaneous structure up to the anal margin, then the mucosa and submucosa, the external and, if necessary, the internal sphincter muscle, must

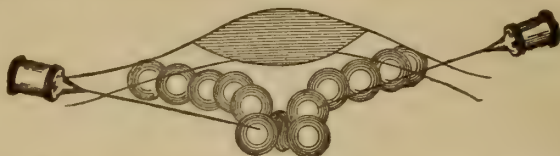


FIG. 4.—SHOWING MODE OF INJECTING THE FLUID UNDER AN ABSCESS IN SUCCESSIVE WHORLS. (Schleich.)

be distended with water slowly injected. In deep rectal operations, involving extensive cutting or curetting, water anesthesia seems not to suffice.

*Centric Local Anesthesia.*—Corning, A. Bier, Seldowitsch, and Tuffier introduced into the practice of surgery the injection of cocaine into the spinal canal for the production of wide-spread anesthesia below the point of injection, and the method has been successfully employed, so far as the absence of pain is concerned, by various



FIG. 5.—SHOWING THE SYRINGE-POINT IN THE PAPILLARY LAYER OF THE SKIN.

surgeons in a large number of major operations in the lower portions of the body. Experience has, however, shown that this method is attended by so much difficulty and danger that it has almost passed out of vogue.

In performing the operation the hollow needle is introduced into the vertebral canal, as in the operation of lumbar puncture, and from one-sixth to one-third of a grain of cocaine is injected, the most absolute antiseptic precautions being taken throughout. Loss of sensation in the lower extremities is usually complete in ten minutes and begins to go off in about an hour. Serious nervous disturbances have been present in a large proportion of the cases and fatal results have been frequent. One surgeon reported five deaths in one hundred intraspinal injections; and, according to H. Mohr-Bielefeld, all available statistics taken together show that one death is to be expected in every two hundred spinal anesthetics.



Much more available for the purposes of practical surgery than is centric anesthesia is the process which may be known as *Neural Anesthesia*. As long ago as 1884 the injection of cocaine into a nerve-trunk for the purpose of producing anesthesia in the region supplied by the nerve was suggested, not very clearly, by Hall and Halstead. In the production of neural anesthesia cocaine has been almost universally employed by surgeons, but whether it has or has not superiority over eucaine has not as yet been determined. The selected local anesthetic is to be injected immediately in contact with the nerve, if it be a small one, or into the nerve-trunk itself if the nerve be large. So injected, cocaine produces a complete break in the conducting power of the nerve, affecting, it is affirmed, not only the fibres which are connected with the pain sense, but all afferent fibres, so that, when the incision is made into the region of the peripheral distribution of the nerve, not only is there no pain, but no surgical shock, all nervous impulses going upward from the lower part operated upon being shut off from the nerve-centres. When the nerve is small and easily reached, the injection of a two-per-cent. solution of cocaine may be made into its sheath without previous incision; but when an amputation or other large operation is to be performed, it is essential to expose under infiltration-anesthesia the one or more nerves involved, and inject a solution of cocaine, which should not be stronger than one per cent., directly into the centre of the nerve. When neural anesthesia is practised, it is essential that the most absolute antiseptic precautions be taken. *A priori*, it might be expected that the process would involve the danger of the production of neuritis, but so far the clinical reports do not indicate that such danger exists.

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### FAMILY III.—SOMNIFACIENTS.

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IN the family somnifacients are placed in this treatise those drugs whose chief use in practical medicine is for the production of sleep. Hyoscine is a valuable hypnotic, but as it is found in plants associated with the delirifacient alkaloids, and is physiologically more closely allied to them than to the somnifacients, it will be considered under the head of Delirifacients.

#### OPIUM.

Opium is the dried juice obtained from the unripe capsule of the *Papaver somniferum*, the white poppy. This plant is a native of Asia, and was cultivated as far back as the time of Homer for the sake of its beautiful white flowers. The medicinal properties of the plant have been known for at least 2000 years, and Dioscorides has related the method of collection of opium, which is practically the same as that of to-day. The plant is extensively cultivated in India, China, Persia, and Asiatic Turkey. Immense quantities of it are produced, the importation of the United States alone being in the neighborhood of one and one-half million pounds annually.

The *Papaver somniferum* is a small herb growing to the height of two to six feet, producing large, showy white flowers of a shape similar to that of our native red poppy. The active ingredient seems to be present in the plant only during fruition. Opium is obtained by incising the capsule (fruit) before it has ripened and allowing the juice to exude for twenty-four hours and then collecting. Several varieties of opium are recognized according to the country from which they enter commerce, as the India opium, the Persia opium, etc. Practically all of the opium which enters the United States comes through the port of Smyrna and is known as Turkey opium or Smyrna opium. It occurs in large, irregular lumps, weighing from a quarter to two pounds, of a brownish, mottled color, frequently with the remnants of poppy-leaves or plants adhering to its surface. It has a peculiar "narcotic" odor and a bitter taste. It is completely soluble in dilute alcohol, and although not completely dissolved, its active ingredients are taken up by water. It is a very complex body, containing the alkaloids morphine, codeine, narceine, narcotine, thebaine, papaverine, porphyroxine, cryptopine, meconine, opianine, and paramorphine, besides meconic, thebolactic, and sulphuric acids, extractive matter, gum, glucose, fixed oils, a volatile odorous principle, and other substances of no importance. Of these substances morphine

is by far the most important and the U. S. Pharmacopœia directs that crude opium shall contain not less than nine per cent. of this alkaloid.

*Morphine* is obtained by precipitation with ammonia water from solution of opium. It is very slightly soluble in water, but, like the other alkaloids, forms soluble salts with various acids.

**Incompatibilities.**—Opium is incompatible with the alkaloid precipitants, as alkalies, tannic acid, corrosive sublimate, iodides, etc. Besides these, on account of the meconic acid, it precipitates the salts of many metals, notably lead acetate (which is the basis of the well-known lead-water and laudanum embrocations).

#### Official Preparations : \*

There are six *solid* preparations of opium:

Opium Pulvis (12 per cent. Morphine) . . . . .	$\frac{1}{2}$ to 2 grains (0.03–0.12 Gm.).
Opium Deodoratum (12 per cent. Morphine). $\frac{1}{2}$ to 2 grains (0.03–0.12 Gm.).	
Opium Granulatum (12 per cent. Morphine). $\frac{1}{2}$ to 2 grains (0.03–0.12 Gm.).	
Pilulæ Opii (Each one grain) . . . . .	1 to 2 pills.
Extractum Opii (20 per cent. Morphine). . . $\frac{1}{2}$ to 1 grain (0.03–0.06 Gm.).	
Pulvis Ipecacuanhæ et Opii [Dover's Powder] (10 per cent. each of ipecac and powdered opium). . . . .	5 to 10 grains (0.3–0.6 Gm.).

The *liquid* preparations each represent ten per cent. powdered opium, except the camphorated tincture. It should be remembered that one minim of tincture of opium is equal to almost two drops.

Acetum Opii (10 per cent.) . . . . .	5 to 15 minims (0.3–1.0 C.c.).
Tinctura Opii [Laudanum] (10 per cent.) . . .	5 to 15 minims (0.3–1.0 C.c.).
Tinctura Opii Deodorata (10 per cent.) . . .	5 to 15 minims (0.3–1.0 C.c.).
Tinctura Opii Camphorata [Paregoric] (Powdered opium, camphor, benzoic acid, oil of anise, each 0.4 per cent.) . . . . .	1 to 4 fluidrachms (4–15 C.c.).
Vinum Opii [Sydenham's Laudanum] (10 per cent.) . . . . .	5 to 15 minims (0.3–1.0 C.c.).
Tinctura Ipecacuanhæ et Opii (10 per cent. of each) . . . . .	5 to 15 minims (0.3–1.0 C.c.).

The following preparations of Morphine are recognized:

Morphina . . . . .	$\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.015 Gm.).
Morphinæ Acetas . . . . .	$\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.015 Gm.).
Morphinæ Hydrochloridum . . . . .	$\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.015 Gm.).
Morphinæ Sulphas . . . . .	$\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.015 Gm.).
Pulvis Morphinæ Compositus [Tully's Powder] ( $\frac{1}{2}$ per cent.) . . . . .	5 to 10 grains (0.3–0.6 Gm.).

The official salts of codeine are:

Codeina . . . . .	$\frac{1}{2}$ to 2 grains (0.03–0.12 Gm.).
Codeinæ Phosphas . . . . .	$\frac{1}{2}$ to 2 grains (0.03–0.12 Gm.).
Codeinæ Sulphas . . . . .	$\frac{1}{2}$ to 2 grains (0.03–0.12 Gm.).

*Local Action.*—The local action of opium and its chief alkaloid appears to be purely sedative.

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\* For morphine derivatives see page 73.



*Elimination.*—Morphine, according to Cloetta, is largely destroyed in the system, but it is also partly eliminated through the various glands, especially the kidneys and the glands of the stomach and intestines.

Morphine has been detected in the urine by Eliasson, Bouchardat, Wormley, and many others; in the alimentary secretions by Orlt, Rosenthal, Binet and Hamburger. The elimination appears to proceed slowly, as Wormley detected the alkaloid in the urine passed three days after its ingestion, and Antheaume and Mouneyrat found it in the body of an opium-eater who had died fourteen days after the last dose. Faust believes the alimentary glands are the most important channels of escape of the drug.

**Physiological Action.**—*Nervous System.*—When opium is taken by man in such dose as to produce its mildest physiological effects, it exerts a quieting influence, inducing a peculiar dreamy condition of bodily comfort and happy content, during which images and ideas float before the mind, and by their endless and effortless repetition shorten the time, which seems to lose itself in rest. It is commonly asserted that there is a stage of the action of opium in which the activity of the mental faculties is exalted. This may be so in those who have accustomed themselves to the use of the drug as a stimulant; but our experience is that in those who do not habitually take opium true mental power is, during all the stages of the action of the drug, diminished rather than increased. The state induced is the fabled calm of the lotus-eater rather than the energetic activity of production. Even in those who are accustomed to the use of opium, as an aid to work, it is probable that the imagination rather than the reasoning faculty is excited by it.

The apparent difference in the effects of morphine upon man and the lower animals depends chiefly upon the different degree of development of the brain and spinal cord. The drug acts as a cerebral depressant and a spinal stimulant, and in the lower scale of life, where the spinal cord is more highly developed than the cerebrum, it produces exaggerated reflexes and convulsions, whereas in the higher mammals, as in man, the cerebral symptoms predominate as is shown by quietness and sleep.\*

In the frog, opium and morphine act similarly, producing primarily a condition of violent tetanus, with great increase of the reflex activity, ending, if the dose has been large enough, in a progressive paralysis with disturbed respiration, and finally cessation of the same. W. Baxt states that when a very minute dose is used (15.25 milligrammes) after a period of heightened excitability there is stupor with increased reflex excitability as it passes off. As was first shown by Kölliker, and abundantly demonstrated since, the tetanus is not prevented by section of the spinal cord, and, with the heightened reflex activity, is therefore due to spinal excitement. It is probable, however, as affirmed by Kölliker, by Albers, and by Meihuizen, that some of the convulsions are epileptiform.

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\* A curious corroboration of the views expressed in this paragraph is found in the following sentence taken from Althaus (*Diseases of the Nervous System*, New York, 1878, 135): "In infants, however, and also in the lower races of mankind, as in negroes and Malays, convulsions are observed after its [opium] ingestion."

S. Weir Mitchell has shown that birds, as represented by pigeons, chickens, and ducks, are very insusceptible to the toxic action of opium and its chief derivative, morphine. The symptoms induced have been very uniform: they are unsteadiness, labored breathing, increasing signs of dyspnœa, *unaltered* pupils, and, finally, general convulsions and death. No true hypnotic effect has been observed, but a curious and very great rise of temperature just before death was noted in one case. As Flourens affirms that a single grain of the aqueous extract of opium will throw a sparrow into a profound stupor, it can scarcely be considered as proved that the drug acts upon all birds as upon those experimented with by Mitchell.

In the mouse, according to the experiments of Harley, the first effect of an injection of from one-twentieth to one-twelfth of a grain of morphine is a tonic cramp-like contraction of the muscles, especially of the trunk, of such character that periods of forced rest alternate with a slow, laborious creep, which seems to originate not in the limbs but in the trunk itself. There is in this state no tendency to somnolency, but, on the contrary, an abnormal sensitiveness to loud sounds, which cause the mouse to resume for a moment active running movements. The breathing is irregular, the pulse accelerated, and finally stupor develops itself, and coma deepens into death by dyspnœa; or, otherwise, recovery, preceded by convulsive movements of the hinder part of the body, is gradually brought about.

According to M. L. Guinard, in the cat morphine produces violent hyper-excitability, great restlessness, agitation, hallucinations, dilated pupils, accelerated heart and respiration, from which the animal returns to its normal condition unless the dose have been very large, when tetanic convulsions develop.

In the horse (Harley) two or even three grains of morphine hypodermically injected produce sometimes a slight drowsiness, sometimes no perceptible effect. Doses of from four to six grains cause great restlessness and accelerated pulse. The mouth is moist, the temperature of the skin and its secretion increased; the animal paws continually, and treads about in his stall with an almost rhythmical movement. After twelve grains, Harley noticed in some cases very great excitement, as shown by marked increase in the rapidity of the heart's action, by muscular rigidity and tremors, and by the animal's walking rapidly to and fro, slobbering and sweating profusely. In another horse, after an immediate strong erection of the penis and copious emission of semen, heavy sleep came on, interrupted after the third hour by the usual symptoms of excitement. Thirty-six grains of morphine acetate caused in a powerful hunter deep comatose sleep, commencing in fifteen minutes and lasting for three hours, when it was replaced by intense restlessness and severe delirium, continuing for seven hours. During this time the animal was perfectly blind. Previously to these studies, Barbier had found that four drachms of the aqueous extract of opium produced violent tremblings, apparent insensibility to external irritants, convulsions without coma, and death. One hundred grains of morphine acetate killed a horse by convulsions in three hours. Ernst Hess has shown that in the ruminants morphine produces first excitement and then narcosis.

Upon dogs\* morphine acts very much as upon man (see Harley, Bernard and Reese). In very many cases, if not in the majority, eight to ten grains of the alkaloid injected into a dog of moderate size will cause deep sleep, amounting to coma, so that the animal will remain in any position in which he may be placed. While in the deeper degrees of this sleep there is marked insensibility to pinching and other forms of external irritation, a repetition of irritation, and especially a sudden loud noise or shaking, will arouse the animal, precisely as in man. Indeed, sometimes the dog, even when comatose, seems more than normally sensitive to sudden noise, trembling and starting in an almost convulsive manner. After awaking, the dog shows unmistakable signs of nervous and psychical depression. In walking, the hind legs are dragged, as though semi-paralyzed; the eyes are haggard; the naturally brave animal cowers in a corner or seeks to hide himself, no longer recog-

\* According to Joffroy and Serveaux (*Archiv d. Med. Exper. Anat. Path.*, 1898, x.), the fatal dose of morphine is: for dogs, intravenously 0.029 gramme per kilo, hypodermically 0.035 per kilo; for rabbits, intravenously 0.15 per kilo, hypodermically 0.25 per kilo.

nizing his master, and does not return to his natural condition for many hours. After smaller doses the effects are proportionately less intense.

*Nerves.*—According to Gscheidlen, morphine primarily increases and secondarily depresses the excitability of the motor nerves of the frog, the period of heightened functional activity not being demonstrable after enormous doses. Albers affirms that depression may develop into complete paralysis of function, though Gscheidlen has never been able to verify this. Gscheidlen further asserts that the local application of morphine intensifies and protracts the excitability of an afferent nerve in strychnine-poisoning. No phenomenon of human poisoning by opium can be attributed to its action on nerve-trunks, but the relief of pain sometimes obtained by the local use of opium would indicate that in concentrated form it depresses the sensory fibres even of human nerves.

*Circulation.*—In man a moderately large dose of opium produces a slight evanescent acceleration of the pulse-rate (see Nothnagel) succeeded by a characteristic slowing and increased fullness and force in the pulse. After toxic doses the slow pulse later becomes exceedingly rapid. In the lower animals large doses produce a slight rise in the blood-pressure followed, after poisonous quantities, by a fall. The slowing of the pulse is due to stimulation of the cardio-inhibitory mechanism, probably chiefly central, although Gscheidlen believes that the peripheral endings of the vagi are also stimulated. The increased rate of the pulse in poisoning is due to paralysis of the peripheral ends of the vagi. The changes in the arterial pressure are due chiefly to its influence upon the heart muscle, the drug acting in moderate quantities as a slight stimulant, in larger doses exercising a depressant influence upon the heart; its action upon the vaso-motor system is uncertain but is probably very slight, if any. The therapeutic dose of morphine in man produces practically no change in the circulation aside from some slowing of the pulse.

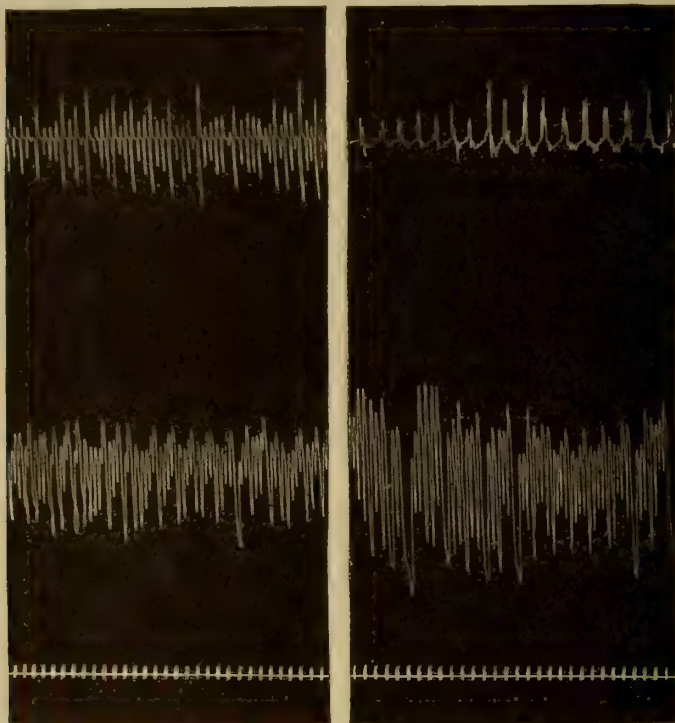
In some individuals therapeutic amounts of the alkaloid may depress the circulation, but, in agreement with Riegel and Preisendorffer, it can scarcely be doubted that therapeutic doses have no sensible effect upon the circulation in the ordinary man. It has been found by M. L. Guinard that in the dog morphine produces primarily a slight rise of the arterial pressure, followed by a fall during the period of narcosis. Ringer and Sainsbury found that opium first increased the power of the isolated heart of the frog, then depressed it and finally caused diastolic arrest.

The slow, full pulse of the second stage of opium-poisoning is due to an action of the drug upon the inhibitory cardiac nerves, for Gscheidlen has experimentally demonstrated that after section of the vagi morphine is powerless to lower the pulse, and also that division of the nerves during the second stage of morphine-poisoning is followed by an extraordinary rise in the pulse-rate. That the peripheral ends of the vagi are stimulated was proved by the fact that cardiac arrest took place when the distal ends of the cut nerve were more feebly irritated than would suffice to affect the unpoisoned animal; and that the inhibitory cerebral centres are stimulated was demonstrated by the instantaneous very great fall of the pulse-rate, amounting in some cases to one-half in less than half a minute, which ensued upon the injection of a large dose of the alkaloid into the carotid,—*i.e.*, into the brain and the inhibitory centres. The rapid feeble pulse of the third stage of opium-poisoning Gscheidlen found to be due, at least in a measure, to paralysis of the peripheral vagi; for at such time stimulation of the peripheral end of the cut nerve was powerless to affect the heart.

The question of the action of morphine upon the vaso-motor system is of great interest, but cannot at present be fully answered. Gscheidlen believes that it first



stimulates and then depresses it, and asserts that after the injection of a large dose the arterioles in the mesentery can be seen to contract, and later (third stage) to dilate. The objections to this sort of evidence are sufficiently stated elsewhere in this book; and the rise of the arterial pressure, which he also adduces as an argument, may be accounted for without calling upon the aid of the vaso-motor nerves. While, therefore, it is probable that morphine does exert the influence he asserts for it, the question must still be considered as *sub judice*: that the vaso-motor system is not paralyzed even *in extremis* is shown by Gscheidlen's experiment, in which electrical stimulation of the cord at such time induced immediate rise of the arterial pressure. The action of morphine upon the brain is certainly independent of any action on the vessels.\*



(Before Injection.)

(After Injection.)

FIG. 6.—THE EFFECT OF OPIUM ON CIRCULATION AND RESPIRATION. Note the great slowing of respiration, also the slowing of the pulse without much change in the blood-pressure.

*Respiration.*—Death occurs from opium, in the great majority of cases, by failure of the respiration; and that such failure is due to a direct action of the poison upon the respiratory centres in the medulla is proved by the fact that morphine affects the breathing of dogs and rabbits whose pneumogastrics have been cut as much as it does those whose nerves are entire (Gscheidlen).

The action of opium or morphine upon the elimination of carbonic acid has been studied by Boeck and Bauer and by Chittenden and Cummins. Their results

\* Consult Binz, *Arch. f. Exper. Pathol. und Pharm.*, vi. 310; Vulpian, *Leçons sur l'Appar. vaso-moteur*, ii. 156.

are concordant in showing that the effect of the alkaloid upon carbonic acid production is in direct relation to its influence upon the muscular system. The elimination is increased when convulsions occur, but decreased when narcotic quietude is produced. According to Reichert, the fall of temperature produced by the toxic dose of morphine is caused by a lessening of heat production, which is due to depression of thermogenic centres in the caudate nucleus. Luzzatto found that under the influence of morphine there is a very marked increase in the destruction of nitrogenous tissue.

*Eye.*—Since morphine locally applied does not affect the pupil, it follows that its contracting action upon the latter is through the nerve-centres. It is probable, but has not, that we are aware of, been experimentally proved, that the contraction of the pupil is, at least largely, due to stimulation of the oculo-motor nerve-centres, and that the dilatation of the pupil as death approaches is due to a paralysis of the same. Indeed, it cannot well be otherwise; for if the primary contraction were due to paralysis of the sympathetic, the secondary wide dilatation would be impossible; the dilating force—*i.e.*, the sympathetic—having been withdrawn, the pupil would not widely expand even if the contracting force—*i.e.*, the oculo-motor—were paralyzed.

In birds (S. Weir Mitchell) the pupil is not affected, probably for anatomical reasons (see *Atropine*). In horses it is widely dilated (Harley); and in dogs it dilates before contracting (Reese, apparently confirmed by Experiment No. 8, Harley), or sometimes remains unchanged (Harley). At present these anomalies cannot be explained.

*Secretions.*—Opium ordinarily checks all the secretions of the body, although this influence is capable of being modified by certain drugs so as to produce a sudorific action. By it the urinary secretion is habitually diminished, owing, as has been shown by Thompson, to a direct action upon the kidneys. Retention, which after a full dose of opium is not rare, depends upon the blunting of the sensibility of the bladder.

*Intestines.*—Opium, and to a less extent morphine,\* has a very pronounced influence upon the digestive tract, in many persons producing nausea, in all lessening the appetite and the activity of digestion and causing constipation. The disorder of digestion and the constipation are in part, at least, due to an arrest of secretion, probably both in the stomach and in the intestines; but they are also probably to some extent due to the checking of peristalsis, an effect which can often be shown in men, and which Nothnagel and Ott have demonstrated upon animals.† According to Magnus, the effect on peristalsis occurs after dividing the plexuses of the nerve trunks passing from the sympathetic system to the intestines. He

\* Vamossy (*Deutsche Med. Wochenschr.*, 1897, xxiii.) has endeavored to determine experimentally why opium causes constipation more than does morphine. He finds, however, that neither narcotine, thebaine, codeine, kryptopine, nor laudanine is equal in power of checking peristalsis to morphine; and that it is not probable that any of them are responsible for the constipating effects of the crude drug.

† The theory of Hirsch, that morphine causes contraction of the pylorus, is very improbable, since, granting the correctness of his experimental results, a more probable explanation is that gastric peristalsis is checked by the alkaloid.

believes the action is upon the plexus of Auerbach. Both Nothnagel and Ott affirm that the toxic dose of morphine in the lower animals increases peristaltic movement, which affords a possible explanation of the diarrhoea sometimes seen in chronic opium-eaters.

**SUMMARY.**—The dominant action of opium is the production of sleep by cerebral depression. The power of relieving pain is as yet not thoroughly explained; probably, however, by benumbing the perceptive centres in the brain. It acts upon the spinal cord of many of the lower animals as a stimulant, but in man this effect is not perceptible. It both slows the pulse and increases to some extent the force of the circulation by an action upon the inhibitory nerve-centres, probably both centric and peripheral, and by a slight stimulant influence upon the heart-muscle or its intrinsic ganglia. It is a centric respiratory depressant; it contracts the pupil by a centric action which is probably that of stimulation of the oculomotor nerve-centres. It lessens all the secretions except the sweat and also diminishes intestinal peristalsis.

**Therapeutics.**—The chief indications for the use of opium are considered below, *seriatim*. Nearly all of them flow evidently from the known physiological action of the drug; others, however, although established by clinical experience, and undeniable, are not so plain in their philosophy.

1. *To relieve pain.*—As an analgesic, morphine is without a rival in the materia medica, except it be the anesthetics. It is used to allay pain arising from any cause whatever, except acute inflammation of the brain, and is preferred to the anesthetics whenever the pain has any permanency. In *painful spasm* it is especially useful, as it seems very frequently to quiet the motor as well as the sensory disturbance.

2. *To produce sleep.*—Sleeplessness occurring in acute disease, and not dependent upon cerebral inflammation, may very frequently be relieved by morphine. While it is often necessary to use the drug freely in such affections as *delirium tremens*, care should be exercised not to overwhelm the nerve-centres by enormous doses. In habitual sleeplessness great caution must be used in the employment of morphine, not so much on account of the disturbance of digestion which it is liable to cause, as for fear of producing the “morphine habit.” Chloral is perhaps a more generally applicable hypnotic than opium. Be this, however, as it may, we have found the combination of morphine and hydrated chloral singularly efficient. In low fevers, adynamic delirium often coexists with sleeplessness, and is then best met by morphine.

3. *To allay irritation.*—In various forms of nervous erethism; morphine is most valuable; but when the affection is at all chronic, the dangers of the opium habit should not be lost sight of. On the other hand, in acute cases, as in the excitement which so frequently attends *hemoptysis*, the drug should be used freely. In many cases



of disease, opium is serviceable by sustaining the system against an irritation for the time being irremediable, by blunting the sensibilities. In this way it is useful in the advanced stages of *smallpox*, and in various surgical affections, in which it also does good by allaying pain. In various local irritations opium is continually employed, as in *colic* caused by undigested food, and in *bronchitis* to quiet cough.

By allaying irritation and pain, morphine affords relief in most cases of inflammation; but in certain varieties of the affection it seems to do much more than this, exerting, in some way at present difficult to explain, a life-saving influence. In *peritonitis*, after due depletion, or in cases not requiring depletion, it should always be exhibited in large doses at regular intervals, in such a way as to keep the patient in a state of decided narcotism.

In severe *acute vomiting*, opium is one of the most reliable remedies. Although, by checking secretion and peristalsis, opium usually causes constipation, yet when *obstruction of the bowels* is produced by spasm due to an irritation or inflammation, by relieving the latter morphine will sometimes act as a most efficient laxative.

4. *To check excessive secretion*.—For this purpose opium is very largely employed in *diarrhœas*, and is very efficient either alone or in combination with various remedies. In *enteritis* and in *dysentery*, although no less frequently used than in *diarrhœa*, it is of service as an antiphlogistic and analgesic rather than by checking secretion. In *diabetes insipidus*, the combination of it and gallic acid has been much used, and is often effective.

In *diabetes mellitus* opium has long been employed as one of the most useful remedies we have for this disease. Meyer reports a case of diabetes due to pancreatic cancer in which opium produced a diminution in the daily output of sugar. While in some cases it appears to have effected a permanent cure, in the majority of instances, like all other known remedies for this disease, it acts simply as a palliative; it must be given in large ascending doses, the patient for the time being made an opium-eater, a procedure justified only by the fatal nature of the malady. In this condition opium is preferable to morphine. Many authorities have claimed to have obtained the same results from codeine with less derangement of the intestinal tract.

5. *To support the system*.—Opium appears in low fevers, and in various protracted adynamic illnesses, to afford actual support to the system in some way not as yet made out. This is especially the case when, from any reason, sufficient food to keep up life cannot be taken or retained. Opium is a valuable remedy for the purpose of protracting and rendering more comfortable life in the aged. When the bodily powers are failing, and various functional disorders are from time to time occurring, it is often possible to check, by the use of opium, attacks which, if allowed to obtain headway, would extinguish the flickering life. Further, in many cases of feeble very old and suffering people the habitual use of opium under careful restric-

tion of the physician is not only justifiable, but necessary if life is to be maintained as long as possible. In such persons the danger of forming an opium habit which shall do injury is reduced to a minimum.

6. *As a sudorific.*—In 1873 A. Loomis stated that in acute *uremia* large hypodermic injections of morphine would control the convulsions, at the same time producing a profuse diaphoresis, which has been confirmed by Fiset. The method of treatment has been largely followed, in some instances with very happy effect, but in other cases has apparently produced death. Whenever the kidneys are seriously diseased the free administration of opiates is attended by much danger, because one of the chief channels through which the opium alkaloids escape from the system is choked up. As a general sudorific opium is used almost exclusively in the form of Dover's powder. (See p. 58.)

**Administration.**—When it is desired to produce the systemic effect, morphine is usually preferable to the cruder preparations of opium. Pills of opium are especially to be avoided because they sometimes become very hard and undergo solution so slowly that their accumulation in the alimentary canal is possible. On the other hand in the treatment of diarrhœa opium will be found to be more constipating than its alkaloid.

Many persons cannot take opium on account of the very great secondary nausea and depression which it produces. It has been supposed that these disagreeable after-effects are due to the narcotine in opium; but this can hardly be, seeing that they often follow the use of the pure alkaloid, morphine. The deodorized tincture of opium agrees with some individuals better than any other preparation of the drug; and, as first pointed out by Da Costa, by giving a drachm of potassium bromide with twenty-five minims of it, the after-effects of the narcotic are often entirely avoided. Nitroglycerin in many cases will also lessen the gastric disturbance.

*Children always bear opium very badly,\** and to them only the weaker liquid preparations should be given. Dover's powder should especially be avoided. It is probable that in its manufacture on the large scale the ingredients are sometimes not thoroughly mixed: at least we have seen cases in which the symptoms caused by it were seemingly so out of proportion to the dose as to suggest that more than the official amount of opium was present.

The dose of opium for an adult is from one to two grains (0.06–0.12 Gm.); for a child a year old, one-twenty-fourth of a grain (0.003 Gm.).

Of the solid preparations of opium the extract on account of its being the most fixed in its strength as well as of its being free from the noxious constituents of opium, and of its solubility favoring

\* In a babe a day old, one minim of laudanum (E. Smith, *Lancet*, 1854), and in one aged nine months, a few minims of paregoric (Wood, *Bost. Med. and Surg. Journ.*, 1858, are said to have proved fatal.

prompt absorption, is the most useful and reliable. Paregoric, because of the camphor which it contains, is more constipating than are the other preparations of opium, and hence is preferred in diarrhoea-mixtures. The deodorized tincture contains no narcotine, and none of the odorous principle of opium and, therefore, is less apt to cause nausea than are the other preparations. Its drop almost equals the minim in size.

**Toxicology.**—After the ingestion of poisonous doses of opium or its alkaloid morphine, there is a period, the duration of which is in inverse ratio to the dose ingested, in which there is a pleasant feeling of exhilaration and languor with perhaps a slight increase in the rate and force of the pulse, and sometimes nausea and even vomiting. The condition of languor passes gradually into a complete sleep. The increase in the pulse-rate, if it occur at all, is only transient. The characteristic symptoms of opium-poisoning at the stage when the case is usually seen by the physician closely resemble those of cerebral congestion, indeed they are sometimes indistinguishable. The patient is asleep but usually can be partially aroused by loud noises, shaking, cold water and other means, but when left to himself immediately drops to sleep again; the pupils are contracted, the face flushed, sometimes slightly cyanosed, the skin is generally dry and warm, respirations are slower than normal but usually fairly deep and regular. When the patient is aroused the respirations become more rapid and the skin regains almost at once its normal color, the pulse is slow, full and strong. Death very rarely occurs during this stage. If the symptoms do not gradually ameliorate the patient passes into a condition of stupor and prostration, the sleep becomes comatose in character so that it is frequently impossible to arouse him, the pupils are contracted almost to obliteration, the skin becomes cold and moist, the face is at once pallid and cyanosed, the respirations extremely slow and shallow and often interrupted by intervals of death-like quiet, the pulse rapid and feeble, and gradually the patient dies with extinction of nearly all the vital functions, although the immediate cause of death is usually respiratory failure.

The most important points in the diagnosis are the equally contracted pupils, the character of the sleep, and the slowness of the pulse and the respiration.

Although the symptoms which have been narrated are those usually produced by opium, yet in certain individuals the drug provokes quite different phenomena. Thus, cases have been reported in which one-fourth of a grain, or a somewhat greater quantity, of morphine, hypodermically injected, has been followed at once by syncope, with struggling for breath, and apparently imminent or even present death.\* A rarer idiosyncrasy exists in those persons who are rendered by opium very delirious, it may be even wildly so. In certain cases of opium-poisoning, partial or complete convulsions have occurred amidst the more usual phenomena.† Severe itching of the skin is a common phenomenon when the action of opium is

\* See Report of the Committee on the Hypodermic Method of Injection, *Medico-Chirurgical Transactions*, i.; see also *Medical Times and Gazette*, 1868, cases reported by Braine and by Roberts.

† Cases, *Brit. Med. Journ.*, 1876, ii. 496; *Pacific Med. and Surg. Journ.*, July, 1876.



going off, and there are persons in whom such violent erythema is produced even by therapeutic doses as to forbid its use. R. V. Jaksch reports temporary blindness as produced by opium. Glycosuria has been noticed both in animals and man (Adler; also Luzzatto).

The positive medico-legal diagnosis of opium-poisoning from the symptoms alone is not possible, even in the most characteristic cases, because the phenomena produced by cerebral congestion, apoplexy, and uremia may be identical with those of opium-poisoning. Inequality of the pupils, which has been considered proof that a case is not narcotism, has been reported by Taylor as present in poisoning. In atypical cases without a history, even the working diagnosis may be very difficult. The spinal symptoms may entirely overshadow the cerebral phenomena; trismus, tetanic convulsions, tonic rigidity of the muscles, spastic gait, marked heightened reflexes, and ankle clonus have been reported by the drug in the adult. In children it is common for the nerve-centres to be at once overpowered by the poison, so that the second stage may be very much shortened or entirely aborted, and collapse with unconsciousness develop almost at once.\*

*Treatment of Opium-Poison.*—Tannic acid is feebly antidotal to morphine, but it has been entirely displaced by potassium permanganate, which rapidly destroys the alkaloid by oxidation. The allegation that potassium permanganate is capable of following morphine into the blood and there destroying it is, *a priori*, improbable, and it has been experimentally shown that the hypodermic injection of potassium permanganate in morphine-poisoning is futile (Sharp and Thornton and Holder). Nevertheless, during the whole narcosis, there should be repeated administrations of potassium permanganate by the mouth for the purpose of destroying morphine excreted into the stomach. Besides the administration of the antidote, the indications in opium-poisoning are to evacuate the stomach, to maintain respiration, and to keep up the circulation when failing. The first of these indications may be met in two different ways: by an emetic, and by the stomach-pump or tube used as a siphon. There is often in narcotic poisoning great difficulty in getting an emetic to act, owing to the obtunding of the sensibility of the nervous system by the poison. For this and other reasons, so palpable as not to need mentioning, only a prompt stimulant emetic should be used. Antimony, on account of its depressing influence, should always be avoided. *Mustard flour* is almost always to be had at once, and is very efficient. A heaped tab spoonful stirred up in a tumblerful of warm water should be exhibited as soon as possible, and, if it fail to act in fifteen minutes, should be repeated; if this fail, a powder of thirty grains each of zinc sulphate and ipecacuanha may be given, to be repeated at intervals of twenty minutes. Large draughts of warm water should be administered in the intervals, and also between the acts of vomiting, so as thoroughly to wash out the stomach. The stomach-pump† is of no value when the solid

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\* For discussion of effect on nursing and fœtus when morphine is given to the mother, see *Amer. Journ. Obstet.*, 1877.

† The *siphon stomach-pump* may be readily extemporized. It consists simply of an india-rubber tube three and a half to four and a half feet in length, of proper calibre, which is passed into the stomach. The external end being elevated, water is poured into it until the stomach is full; then, without the tube being allowed to empty itself, the external end is dropped, when, of course, the flow of water is reversed.

drug has been ingested, but, if at hand, is preferable to emetics when a liquid preparation has been taken, because of the promptness and thoroughness of its results.

To maintain respiration is the ultimate object of all the measures which are commonly undertaken for the purpose of arousing the system in opium-poisoning. Unconsciousness in itself is of no moment, but as it deepens the sensibility of the respiratory centres grows less, and consequently the involuntary breathing is less rapidly or less perfectly performed. More than this, when at all awake, a patient suffering from opium-poisoning can be made to supplement the almost suspended automatic breathing by voluntary respiration, and every effort to induce him to do this should be used. It is often surprising how an apparently unconscious man can be made to breathe by a command shouted in his ear. To keep a patient awake, walking, flagellations with small, *fine* twigs, shaking, shouting, and various other methods which may suggest themselves, should be practised. Care should always be exercised not to carry these useful measures unnecessarily far, and perhaps add physical exhaustion to the natural prostration of the third stage. The strong faradic current offers a means of causing pain, and therefore of rousing the patient, without leaving bruises or other after-effects.

The cold douche is also an excellent method of rousing the patient and at the same time of especially stimulating respiration. The simplest method of application is to support the head and shoulders of a patient, stripped to the waist, over a common wash-tub, and to dash the water over the chest and head. The effect is much greater if ice-cold water and water a little hotter than the hand will bear (115° F.) be used in quick succession. Very strong coffee has been used from time immemorial, and may be substituted by the alkaloid caffeine. The alkaloids which are to be relied upon, however, are strychnine, cocaine, and atropine, and of these the most valuable is probably strychnine, next cocaine.\* The alkaloids should be given hypodermically, in moderate doses at short intervals, until some effect is manifested upon the respiration. The pupil is not a safe guide as to the administration of atropine, which alkaloid should, indeed, never be given in very large doses. In all cases it is better to use two or more of these alkaloids than larger doses of any one. When in advanced stages the circulation fails, digitalis and strychnine are the chief remedies, but alcohol may be used carefully, the danger being that any excess of it may aid in depressing the heart. In severe cases it is wise to give digitalis hypodermically before the

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\* The value of strychnine as a respiratory stimulant in various forms of narcosis was first demonstrated in the laboratory by H. C. Wood, and subsequently cases were reported by Clara Derum (*U. M. M.*, 1870) and others.

In regard to the value of atropine, E. F. Bashford (*A. I. P.*, 1901, viii.) confirms its usefulness in opium-poisoning; while in a very elaborate paper E. T. Reichert (*T. M.*, 1901) reaches the conclusion that very frequently the overdosing of cases of morphine-poisoning with atropine has contributed to the fatal result, and that it is only of use as a respiratory and stimulating agent before the third stage of the poisoning is reached; and further, that, on account of its in many ways synergizing with morphine, it is dangerous when given in overdose. In these conclusions Reichert seems to us correct.

For cases in which cocaine was used in opium-poisoning, see *Amer. Med. Journ.*, 1901.

end of the second long stage, so as to get its stimulating influence upon the heart in the coming depression.

As the result of numerous experiments, E. T. Reichert reaches the conclusion that cocaine is almost completely antagonistic to morphine, combating the influence of the morphine not only upon respiration and circulation, but also upon the general metabolism, and synergizing with the morphine only in its action upon the spinal cord. He finds that, on the whole, it acts more powerfully upon morphinized than upon normal dogs.

In bad cases of opium-poisoning the use of artificial respiration should not be postponed. In some cases the Sylvester method may suffice, but, as was first shown by Fell, forced respiration (see page 48) should be resorted to whenever respiration fails. Fell has reported recovery obtained in this way after the ingestion of thirty-three grains of morphine. So long as any movement of the heart continues, the forced respiration should be steadily maintained. Inhalations of oxygen apparently saved life in a case reported by Playfair. In some cases the lungs become filled with bronchial mucus; under such circumstances good may be achieved by placing the patient in an inverted position. It is often essential to keep up the temperature of the body by artificial means. Lauder Brunton and Cash have found that the fall of temperature in the poisoned mammal is not prevented by placing the animal in a temperature a little below that of the body, and the ordinary methods used in the sickroom to heat the cooling human body are of very little service. The hot bath or a water bed, two-thirds filled with water of the temperature of 150° F., may be employed. The subcutaneous or intravenous injection of normal saline solution has proven of value in desperate cases; the solution probably aids in the elimination of the poison and the maintenance of the circulation.

Opium-poisoning usually has no sequelæ, but amaurosis and glycosuria have been reported.

In regard to the amount of opium which will cause death, the smallest fatal dose in the adult on record is one-sixth of a grain of morphine.\* According to A. Calkins, four grains† of crude opium placed in the ear have caused death; also four grains by the mouth in more than one case. According to the authority just quoted, out of twenty-nine reported cases in which a fluidounce of laudanum was taken, nine died. The maximum doses from which recovery has occurred without emesis are fifty-five grains of the solid opium and six ounces of laudanum. The death of an adult female has been attributed, with doubtful accuracy, to thirty grains of Dover's powder, given in divided doses. Recovery is asserted after eighteen grains of morphine without vomiting (William C. Chaffee), thirty grains with vomiting (Playfair), and even thirty-three grains (Fell).

\* A number of cases are on record in which death has been produced in the adult by the hypodermic use of from one-sixth to one-half grain of morphine. Consult *Chicago Med. Examiner*, May, 1878; *Quart. Journ. Psycholog. Med.*, 1868, ii, 739; also *Bost. Med. and Surg. Journ.*, 1885, i.

† Taken from the *Journal de Chimie*, 1831. Assuredly there is a mistake in this case.



*Morphine Habit.*—For full details as to the results of the habitual use of opium or its alkaloid, the reader is referred to the treatise of Albrecht Erlenmeyer (*Die Morphiumsucht*). No confidence can be placed in the statements of the opium-eater, and it is essential for cure that such person be in a hospital or be confined to an apartment under the care of an absolutely reliable nurse, so that the orders of the physician can be strictly enforced. The basis of the treatment must consist in the withdrawal of the narcotic, and there are three distinct ways in which this can be effected. First, the opium may be suddenly taken away; secondly, it may be taken away rapidly, but not suddenly; thirdly, it may be withdrawn very gradually. The first of these methods is undoubtedly in most cases efficient, but is often attended by grave danger of collapse, and has no distinct advantages over the plan of rapid withdrawal. The time required for the very gradual withdrawal of the remedy is too great for practical purposes, and the sufferings of the patient are too long drawn out. Unless the daily dose has been extraordinary or the patient is in a very feeble condition, it is safe to withdraw the narcotic entirely in from seven to twelve days. A convenient plan is to direct that a solution of morphine or opium be prepared, and whenever a dose is taken out an equivalent amount of water be added. The chief symptoms that follow the rapid withdrawal are excessive malaise, insomnia, complete loss of appetite, vomiting, diarrhœa, and great feebleness. We have never yet seen a case in which these symptoms were so uncontrollable as really to cause alarm for the safety of the patient. Much may be done by proper feeding. The food should consist of highly nutritious, stimulating, and easily digested articles, and in severe cases should be liquid, such as milk, rich soups, etc. When the circulation fails, alcohol may be used, and much relief may be afforded by massage, and often by simple rubbing of the patient. General electrical stimulation and faradization of the muscles is often useful, not only by its effect upon the circulation, but also by distracting the attention of the patient from his sufferings. The use of the alkaloid cocaine as a stimulant has been recommended. Good results may be obtained from the free internal administration of the fluidextract of coca, but the use of hypodermic injections of cocaine seems hardly justifiable, as the danger of setting up the cocaine habit is too great. If gastro-intestinal irritation exists, bismuth may be administered freely. The diarrhœa is usually controllable by mild vegetable astringents, especially if combined with sulphuric acid. If the bodily temperature falls at all, it must be maintained by external warmth. Potassium bromide, ammonium valerate, compound spirit of ether, and other similar feeble nerve-sedatives may be employed and give some comfort. Moral support and stimulation are essential, and massage or other device which aids in passing the time of suffering is most beneficial.

*Opium-Smoking.*—The various nations of the Orient use opium as an intoxicant by smoking in one of two ways. In Turkey and

neighboring countries it is placed upon tobacco, in a small pipe. In the East it is usually made into a thick, almost plastic, liquid, a large drop or ball of which is held over the flame of a small oil lamp, and the resulting fumes inhaled through pipes of various forms. For an elaborate study of the chemistry of the opiums used in various countries, see *Apotheker Zeitung*, 1903.

Moissan has found in the smoke of opium: morphine, pyrrol, pyridine and various homologues, acetone, and various hydropyridine bases, all of which are physiologically active. This analysis has been confirmed by Hartwich and Simon, who believe that the activity of the opium smoke depends not so much upon the morphine as upon the other products of the destructive distillation.

CODEINE.—According to the statements of various observers, codeine produces, in the lower animals, symptoms very similar to those caused by morphine, —namely, in the frog, heightened reflexes, tetanic cramp with convulsions, also coma; in the pigeon, restlessness, disturbances of respiration, violent convulsions; in the dog, disturbances of respiration, languor, convulsive twitchings, also sleep. For detailed discussion of the observations of various investigators, see tenth edition of this work.

In man codeine is a very uncertain and feeble hypnotic, whose action, especially after large doses, is sometimes attended by marked restlessness. The statements of various clinicians as to its effects and practical value vary very greatly, the variance probably depending largely upon the quality of the codeine used, in many cases the drug exhibited having in all probability been contaminated with morphine. In S. Weir Mitchell's experiments upon himself five grains produced no symptoms except slight increase in the pulse-rate, nausea, some giddiness, and a sense of heaviness about the head; results which are in accord with the earlier experiments of Harley. Contrariwise, A. S. Myrtle records a case of severe poisoning caused by four grains of codeine. There was first vascular excitement and exhilaration, then depression with great anxiety, nausea and vomiting, pale, cool, clammy skin, slight contraction of pupil, and sleeplessness, with slight delirium. Two cases of serious poisoning by eight grains have been reported.\*

In our experience codeine has proved to be a practically useless remedy except for the purpose of controlling *bronchial irritation* in phthisis and other diseases.

In former editions of this treatise the non-official opium alkaloids *narceine*, *narcotine*, *thebaine*, *papaverine*, *laudanine*, *porphyroxine*, *anarcotine*, and *cryptopine* were discussed at length, but, as they have failed entirely to come into use as therapeutic agents, their consideration is here omitted: a full summary of our knowledge of their physiological action may be found in the tenth edition of this work.

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\* See *Brit. Med. Journ.*, 1888, ii., and *New York Med. Record*, 1893, xlv.

## MORPHINE DERIVATIVES.

Various derivatives of the alkaloid morphine are physiologically active, but only two of them are at present used, *Peronine* (morphine benzylester hydrochloride), an account of which may be found in the eleventh edition of this book, having fallen into complete desuetude.

**DIONINE** (*monoethylester of morphine hydrochloride*) is a white crystalline powder, soluble in seven parts of water. Although no careful physiological research has been made upon it, it appears to share to a slight extent the analgesic and hypnotic powers of morphine, and not ordinarily to produce nausea, constipation, or other disagreeable after-effects. It is affirmed to be more active than morphine in the suppression of cough, and to be also actively anti-hydrotic, so that it is of especial value in advanced *pulmonary tuberculosis*. It has also been commended in *asthma* and as an anaphrodisiac; also in *dysmenorrhæa*. The dose is from one-quarter to one-half grain (0.015–0.03 Gm.) in powder, pill, or solution. The general professional verdict seems to be that, on the whole, it resembles heroine in its therapeutic value, but is less powerful.

**Ophthalmic Uses.\***—As first noted by Wolffberg, one drop of a two-per-cent. solution of dionine placed upon the conjunctiva immediately produces smarting and burning pain, free lachrymation, marked injection of the conjunctival blood-vessels, chemosis of the conjunctiva, and occasionally swelling of the lid. This “dionine reaction” varies very much; sometimes it almost fails to appear. Under these circumstances a stronger solution, for example, five to ten per cent., will usually avail, or, according to Darier, an even more active effect may be produced if a morsel of powdered dionine is used, or if the solution is injected beneath the conjunctiva. The irritative effects of the drug are at times exceedingly violent, and Darier believes that the œdema of the conjunctiva, and, moreover, one that spreads to the lids and tissues of the face, is more pronounced in the subjects of vascular disease, nephritis and scrofula. The dionine reaction takes place in the normal as well as in the diseased eye. Usually it subsides materially within an hour. It may continue for a number of hours, although the pain and smarting almost always disappear in a very short space of time, to be followed by a period of analgesia lasting for several hours.

The phenomena of dionine reaction have been aptly described by Wolffberg by the term “lymphatic inundation,” and Darier, who is particularly enthusiastic in his recommendation of the value of this medicament, thinks that lymphatic inundation washes out not only the surface of the eyeball but also the subconjunctival and intracorneal lymph-spaces, and perhaps even the intraocular spaces. There is, according to this author, not only an afflux of liquid but also of lymphocytes, whose duty he believes is concerned with the defence of the parts, so that there is a more active production of antitoxins and phagocytes. Whether the drug really has an action upon the diseased processes of the eye themselves and aids its resolvent power by a subtraction of pathologic fluid, or whether its influence should be regarded as that of a counter-irritant, or whether it depends upon its power of increasing lymphatosis, has not been decided, and at present it is probably not possible to say that it does more than stimulate the lymphatic and vascular circulation of the eye. So far as I am aware, the only untoward recorded result from

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\* This account of the local action of dionine was written by Prof. George E. de Schweinitz.



its action is one case of macular hemorrhage in practice. Violence of reaction without ultimate bad results is not an uncommon phenomenon.

Its indications in ophthalmic therapeutics are numerous, and in general terms it may be stated that it has a favorable influence in alleviating painful inflammations of the anterior portion of the eye, and in relieving the distress incident to increased intraocular tension, that is, *glaucoma*. There is much evidence to show that it facilitates the absorption of atropine, eserine, pilocarpine, etc. It is useful in *iritis*, *irido-cyclitis*, simple and infected *corneal ulcers*, *herpes of the cornea*, *superficial and parenchymatous keratitis*, and in the various types of *glaucoma*. There is some evidence that it is of value in deeper inflammatory processes, for example, in *uveitis*, and it certainly relieves *post-operative inflammation and infection*. It would seem, according to an observation of Dr. Callan, which I think I can confirm from personal experience, that it facilitates the regeneration of corneal tissue. It may be suitably combined with cocaine, atropine, eserine or pilocarpine where these drugs are also indicated; but I believe that a better result is reached if the dionine is used separately, and the atropine, cocaine, etc., is instilled immediately afterwards. In a very brief time, usually after the third or fourth day of its use, the eye establishes a species of immunity, and the dionine reaction almost fails to appear. Therefore, it should be used for two or three days, and then omitted for three days, when again the reaction is likely to appear; or, if it does not appear, the strength of the solution may be increased.

It is the practice of some surgeons, following Darier's recommendation, to use a five-per-cent. solution. If, however, this occasions too much reaction, in my own experience a one-per-cent. solution acts favorably, and I have almost abandoned the employment of the stronger preparations, except when a very decided reaction is desirable, or when immunity has been secured. Instead of employing dionine in solution, it may be used in powder, for example, a twelfth of a grain (0.005 Gm.), or the powder may be dusted directly upon an ulcerated surface. With this method of employment, recommended by Darier, I have had little experience. I have also not prescribed it as a salve, although this method of employment has been advised and commended by others. Darier has used it subconjunctivally, combining it with a physiological salt solution under these circumstances, by injection. The reaction is very violent; but, for example, in *detachment of the retina*, is said to be of service.

The asserted power of dionine of clearing up *corneal scars* I believe to be doubtful, but it certainly is effective and very useful in certain interstitial deposits, such as those of *interstitial keratitis*, both in the early and in the late stages of the disease. The solutions should be freshly prepared to be of service.

**HEROINE** (*diacetyl ester of morphine*), which occurs as a colorless, odorless, bitterish crystalline powder, is nearly insoluble in water, but forms a hydrochloride which is freely soluble both in water and in alcohol. According to Dreser, confirmed by Strube, it produces in the lower animals stupor with convulsions, but has very little influence upon the circulation. Ott has found that in the frog it lessens reflex activity, and in sufficient doses causes complete paralysis which is independent of any effect upon the motor nerve or muscle.

All observers are in accord that it has very little action on the circulation. According to Ott, in doses of from one-twentieth to one-tenth of a grain it produces in the rabbit slight elevation of the pressure without much change in the pulse-rate. The dominant action of heroine is upon the respiratory centre. Impens, Marshall and Fonteyne state that in small doses it slows the rate but slightly increases the depth of the respiration, while in large amounts it lessens both the frequency and the depth. According to Impens, heroine

does not diminish the irritability of the respiratory centre towards carbonic acid, as do both morphine and codeine; this statement is, however, in direct conflict with Dreser.

From the experiments of Impens and Mayor there can be little room for doubt that, at least as regards the lower animals, it requires less heroine to kill than it does morphine. It is probable that this statement holds true also for the human being. As has been pointed out, however, by Impens and by Morel-Lavallee, heroine is a less dangerous drug than morphine, because the efficient dose is proportionately smaller than the fatal dose in comparison to morphine. In other words, although it requires about half the quantity of heroine that it does of morphine to kill, it requires only about one-fourth of the quantity to exercise its maximum sedative effect upon the respiratory centre.

Toxic symptoms following the use of heroine are uncommon. Two and a half grains are said to have produced in an asthmatic adult syncope, myosis, blindness, and subnormal temperature, lasting for many hours, and Dover reports great prostration, dilated pupils, with mental aberration, produced by three grains. Thompson reports death in a case of severe mitral disease, which he attributed to heroine. In a few instances nausea and vomiting have followed the use of heroine, perhaps due, as claimed by Robinson, to some chemical change in the drug. In a number of cases heroine has caused constipation.

As an hypnotic or analgesic heroine is certainly very much inferior to morphine, but it has the advantage that in chronic cases it does not produce the agreeable sensations which render the latter drug so dangerous. In arresting cough it has seemed, in our experience at least, equal to morphine in activity, and has the great advantage of not checking secretion either in the lungs themselves or in the alimentary canal. According to Strauss, it has distinct anaphrodisiac properties, making it useful in various forms of sexual excitement, such as *nymphomania* and *masturbation*. It has been recently asserted, especially by E. Elischer, that it is so active as a local analgesic that one-quarter of a grain introduced into the vagina will relieve the suffering even of *uterine cancer*. Rosenberg commends a two and a half grains to the fluidounce solution as a local anesthetic in diseases of the throat, and especially in *laryngeal tuberculosis*. When there is excessive cough, as in *asthma*, *bronchitis*, and *whooping-cough*, heroine is a very valuable drug; in *phthisis* it has the further virtue of reducing the tendency to sweating. Dose, from one-tenth to one-third of a grain (0.006–0.02 Gm.). The hydrochloride may be used hypodermically.

### HYDRATED CHLORAL.

*Chloral*, or trichloraldehyde ( $C_2HCl_3O$ ), which is itself not used in medicine, is an oily liquid giving off, at the ordinary temperature, pungent fumes, made by the action of chlorine on alcohol. It unites with one molecule of water to form a hydrate.

*Hydrated Chloral* is a volatile, crystalline solid, of a hot, burning taste, freely soluble in water, ether, and alcohol. It usually occurs as transparent, colorless tablets, but sometimes in acicular or even in rhomboidal crystals. If an alkali be added to a solution of hydrated chloral, it breaks up into formic acid and chloroform.

Chloralum Hydratum.....10 to 20 grains (0.6–1.3 Gm.).

*Local Action.*—Hydrated chloral is distinctly germicidal and antiseptic, and was at one time used to some extent for preserving cadavers, keeping urinals pure, and allied purposes. As shown by Keen, a solution of twenty to forty grains to the ounce will preserve animal tissues almost indefinitely without interfering with their microscopic structure. It is also somewhat irritant in its action, and after a time sedative to the sensory nerves, and, it may be, to all tissues.

*Absorption and Elimination.*—Hydrated chloral is absorbed with great rapidity, its action being often manifested within five minutes after its ingestion. It circulates through the body as chloral; its exact fate in the system has not been determined, but it probably escapes from the body in part unchanged and in part in the form of compounds. It was recognized in the urine by A. Tomaszewicz by means of the delicate isocyanphenol reaction\* of Hoffmann. Feltz and Ritter found in the urine of chloralized animals, a copper reducing substance which Von Mering and Musculus have separated, as *urochloralic acid*, in colorless, shining needles, often arranged in star-like groups, soluble in water and in alcohol, insoluble in ether. The existence of this acid has been confirmed and its chemical properties studied by A. Borntraeger and by E. Külz, who found it to be physiologically inert.

*Physiological Action.*—*Nervous System.*—The most constant and prominent of all the symptoms produced by moderate doses of hydrated chloral is sleep, due to a direct depressant action upon the higher cerebral centres. The drug seems also to affect the psychomotor area but sensation is not affected except after toxic doses. Generally, as already stated, the sleep is quiet, but sometimes it is restless, and in man has occasionally even been wildly delirious, although it is somewhat uncertain whether the latter condition may not have been due to impurities in the drug. It seems to be well established that in the milder degrees of this sleep there is no anesthesia. We have seen the hyperesthesia† spoken of by Demarquay after small doses of chloral, and there can be no doubt that it is an occasional, if not a constant, phenomenon. Rajewsky states that there is in frogs a corresponding period of over-excitability of the reflex centres,

\* Many chemists have failed to find chloral for want of a delicate test. F. Ogston (*Edin. Med. and Surg. Journ.*, xxiv. 292) affirms that ammonium sulphide affords a means of recognizing minute amounts of the drug.

† Bouchut (*New York Med. Gazette*, Dec. 1870), Dieulafoy and Krishaber (*Amer. Journ. Med. Sci.*, Jan. 1870), Giovanni and Ranzoli (*Schmidt's Jahrbücher*, cli.), and Rajewsky (*Ibid.*) confirm this, while Liebreich and Labbé deny it; Hammarsten, who has noticed such hyperesthesia, is inclined to think it apparent rather than real.



and that in rabbits he has noticed a glowing heat borne without much complaint, when pinching would produce violent outcries. In *very large* doses chloral produces anesthesia; but, unless the amount employed be so great as to be toxic, this anesthesia is in most cases very trifling.

The paralysis and loss of reflex excitability induced by chloral are spinal in origin and are not due to any action on either peripheral nerves or muscle.

Labbée has shown that the muscles respond to electrical stimulation of the nerve, and also directly of the muscles, even after fatal doses. The experiments of Rajewsky has confirmed the retention of irritability of the motor-nerve and has also found that in the latter stages of chloral-poisoning direct irritation of the spinal cord gave rise to much less severe spasms than in the unpoisoned animal. Before this paralytic stage is reached, as already stated, Rajewsky affirms that in the frog there is a period of increased reflex activity, and that at this time stimulation of the spinal ganglia shows that they are more susceptible than normal. The observer last named states that these phenomena occur just as freely after destruction of Setschenow's centre in the frog as before, and are therefore independent of it.

*Circulation.*—The administration of hydrated chloral in any dose large enough to affect the circulation produces a fall of blood-pressure with usually slowing of the pulse-rate. The fall of the blood-pressure is due largely to a depressant action on the heart although after large doses there is also complete paralysis of the vaso-motor mechanism.

In man, Bouchut and Anstie and Andrews obtained sphygmographic traces which they think indicate a primary increased arterial tension, but Nancias, of Venice, has found the tension normal. Preisendorfer, in a series of sphygmographic studies, thought that there might be a brief primary rise of arterial pressure in man, as in animals, but under the full action of chloral the arterial pressure steadily sinks. We do not think that much confidence is to be attached to these observations, since the sphygmograph seems to be an entirely unreliable instrument when used for the comparative study of arterial pressure. Both Rajewsky and David Cerna have found that chloral, in whatever dose, produces no rise in pressure but always, if the quantity given is sufficient, a lowering, so that if any rise of pressure (as seems improbable) is ever produced in the normal man or animal by chloral, such rise must be indirect and, probably, due to respiratory disturbance. The fall of blood-pressure is probably owing in part to the vaso-motor paralysis, but perhaps in largest part to depression of the heart. The vaso-motor palsy is probably chiefly caused by an action upon the dominant centre, but Kobert has shown that there is also, after a very large dose of the chloral, palsy of the coats of the vessels.

The lessening of the pulse-rate Cerna believes to be due to an influence upon the cardio-inhibitory centres, but Rajewsky asserts that the slowing occurs in the frog and rabbit after section of the pneumogastric nerves and is, therefore, not due to central inhibition. When toxic doses have been employed, the heart, after numerous pauses, is finally arrested in diastole. Analogy indicates very strongly that this arrest is due to a direct influence upon the heart-muscle or ganglia, and the researches of Sidney Ringer and H. Sainsbury and of David Cerna seem to demonstrate (the contrary results obtained by Labbé notwithstanding) that when chloral is brought in direct contact with the isolated heart of the frog there is an immediate and persistent loss of power, ending finally in diastolic arrest. In poisoning in man, the pulse has towards the last been very feeble, generally rapid and irregular, and even in some cases in which recovery has occurred it has been altogether absent for a time.

*Respiration.*—In full doses, chloral lessens the number of respirations per minute, causing them to become slow and full; when toxic doses are taken this action becomes more and more marked, the rhythm is much affected, and the respiration grows markedly irregular, and sometimes very rapid and shallow, until it ceases. As these phenomena occur equally after section of the vagi (Rajewsky), the influence of chloral must be exerted upon the respiratory centre.

*Tissue Change.*—Charles Richet has found that toxic doses of hydrated chloral reduce very greatly the elimination of carbonic acid, at the same time that they lower the bodily temperature. So far as large doses are concerned, A. Gritzka is in accord with this, although he asserts that small doses increase carbonic acid elimination. It is plain that the profound muscular quiet produced by chloral must lead to lessened oxidation. Julius Peiser affirms that chloral increases the degeneration of albuminous tissues.

*Abdominal Action.*—Clinically hydrated chloral has no perceptible action upon the gastro-intestinal mucous membrane, save as a local irritant; but, according to the experiments of Wertheimer and Le-page and of Charles Dubois, it increases in the animals both pancreatic and biliary secretion, chiefly, but not altogether, as the result of its local influence in the duodenum and jejunum.

*Temperature.*—A most remarkable action of hydrated chloral is upon the temperature: in this point all observers are in accord with Richardson, of London, who has seen the temperature fall 6° F. in a rabbit which recovered. Bouchut has noticed a fall of 2° (C. ?) in an infant, and Da Costa and other observers have noticed slighter reductions of temperature in man after therapeutic doses. In a case reported by Levinstein, after six drachms of hydrated chloral the temperature rose to 39.5° C. (102.1° F.), and subsequently fell to 32.9° C. (91.22° F.). Hammarsten has found that the fall of temperature is very rapid, 6° C. in an hour, and that it occurs in animals well wrapped up and laid in a warm place.

**SUMMARY.**—Upon the cerebrum hydrated chloral acts as a powerful hypnotic; in full doses it acts as a depressant upon the centres at the base of the brain and upon the spinal cord: it causes slowing and weakness of the heart's action, and probably vaso-motor paralysis, also centric slowing of the respiration, with loss of reflex activity, muscular weakness, and some anesthesia, all of spinal origin; in fatal doses it usually produces a gradual death by paralyzing the respiratory centres in the medulla, although in rare cases it kills suddenly by directly paralyzing the heart, which always stops in diastole. On the vagi and on the motor nerve-trunks it has no marked influence.

*Action as Chloral.*—Liebreich was led to the discovery of the value of chloral as a practical medicine by the knowledge of the fact that it is converted when in solution by alkalis into chloroform and formic acid, and the expectation that chloroform would be generated by the alkalinity of the blood. This theory, which at one time held, has been so completely disproved as almost to have been lost sight of. A discussion of it may be found in full in the tenth edition of this treatise.

**Therapeutics.**—The results of the clinical use of hydrated chloral are in strict accord with its known physiological action. The indication which it most usefully meets is to induce sleep. The more purely nervous the wakefulness the more successful the remedy. When from functional over-excitement of the brain due to excessive mental strain, or from anxiety or other kindred cause, the patient cannot sleep, hydrated chloral is, probably, the most certain of the hypnotics. On the other hand, when severe pain causes wakefulness, it is of very little value,—at least in doses which we think safe. Sometimes even in these cases sleep will come, but it will very often be a restless, troubled sleep, with moaning or other indications of suffering; and it may be that the patient on awaking will complain that he has suffered more while sleeping than when awake.

In the *sleeplessness* occurring at times during convalescence from acute disease chloral is very efficacious. In the early stages of *fevers* it is sometimes of advantage; Russell recommends it especially in the wild delirium of *typhus* in its earlier stages. In advanced fever-cases, when the symptoms are gravely adynamic, we believe that the use of chloral would be very perilous. In *delirium tremens* it often induces sleep readily, but not rarely it fails, even in large dose. In the sleeplessness of acute puerperal or non-puerperal *mania* there is abundant testimony to the value of chloral. It must not be forgotten that chloral is a dangerous remedy when there is cardiac weakness; and when in any of the diseases just spoken of there is reason to suspect a fatty or even a feeble heart, great care must be exercised in its administration. Under such circumstances the dose of fifteen grains (1 Gm.) should not be exceeded, and should not be repeated more than once unless after an interval of several hours.

The second indication to meet which hydrated chloral may be employed is to *relax spasm*. For this purpose it has been used with advantage in *puerperal* and *uremic convulsions*. It must be remembered that in many of these cases, although next to chloroform the best palliative, it is only a palliative, and must be used merely to quiet the nervous disturbance until other remedies can have time to act. In *tetanus* it is one of the most valuable agents we have for controlling the convulsions, but it must be given boldly and at short intervals. Extraordinary results have been obtained by Macnamara in tetanus by using hydrated chloral simply at bedtime (forty grains), with an occasional dose (thirty grains) in the morning when there is high temperature; and administering brandy, milk, and eggs very freely during the day.

In *trismus nascentium*, as originally recommended by Widenhofer, it is undoubtedly very valuable. Widenhofer gave it to the young babe in one-and two-grain doses by the mouth, or, when the spasms prevented, in double the quantity by the rectum. In *chorea* it is not directly curative, but is of great importance when it is essential to temporarily check the violence of the movements. As a nocturnal quietant and hypnotic, it is of the highest value in cases of acute



chorea in which speedy death is threatened from the incessant and violent movements; also in cases complicated with fractures, where a temporary lull is of importance. In *puerperal convulsions* its use in large doses has met with a great deal of favor. A half-drachm may be exhibited at once, and half the quantity every hour or two *pro re nata*.

In the *convulsions* of children it has been employed with apparent good; in *cramps*, in *singultus*, in the spasmodic *nocturnal enuresis* of children, in *laryngismus stridulus* and other spasmodic affections of the glottis, in *nocturnal emissions*, in *whooping-cough*, and in all forms of severe spasmodic disorder when it is desired temporarily to suppress the motor disturbance, chloral remains the standard remedy. In *asthma* it has sometimes been of use, but more often it has failed. Its hypodermic use in the algid stage of *cholera*, as recommended by Dr. Hall, appears to us of very doubtful value.

The third indication for which chloral has been used is to *relieve pain*. That it will do so when given in very large doses there can be no doubt; but, unless the dose be so large as to be dangerous, it is of little value as an analgesic. Its powers in this direction are incomparably less than those of opium, and its habitual use is attended by grave dangers.

As originally suggested by Lyon Playfair, hydrated chloral may be given in the early stages of labor to lessen the severity of the pain; it is stated also to be of service as a relaxant when there is rigidity of the os. Fifteen grains may be administered and repeated in half an hour if necessary.

Locally a solution of chloral (ten per cent. to saturation) has been used with asserted very good effects as a stimulant and antiseptic in *foul ulcers*, *buboes*, *bedsores*, etc., especially when the discharge is free,—as a hemostatic when there is oozing of blood,—and as an antiseptic and local anesthetic in *uterine* and other *cancers*. Applied to the skin, it is a powerful irritant, and has been proposed as a vesicant,\* but is said to cause excessive pain.

The intravenous injection of chloral, as suggested by Oré, for the purposes of anesthesia, and for the combating of *tetanic spasms*, is entirely unjustifiable and is at present rarely practised, death having in various cases resulted from the unexpected violence of its action or from the coagulation of the blood which is produced.

**Administration.**—Although the continuous use of hydrated chloral may lead to a very serious chronic poisoning, we have no knowledge that the chloral itself accumulates largely in the system. On the other hand, the single large dose of hydrated chloral in rare cases acts with unexpected violence, and it should, therefore, never be given in doses of over twenty grains, and this amount should not be

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\* According to Bonnet (*Union Pharm.*, xlii. 490), one gramme of hydrated chloral rubbed up with oil of sweet almonds or vaseline and spread on a diachylon plaster twelve by fifteen centimetres and placed on the skin, will in fifteen minutes cause burning pain, after which time it should be removed and the part covered with cotton wool. During the sleep, which usually follows the absorption of the chloral, a blister will form.

repeated oftener than once an hour, and, when sixty grains have been taken, not again for some hours, unless in very urgent cases, as acute tetanus or violent chorea threatening speedy dissolution.

Reynolds reports a case in which forty-five grains caused most alarming symptoms and H. W. Fuller a number of cases in some of which very alarming symptoms followed the exhibition of thirty grains, and in one, death in a healthy young woman of thirty. Schwaighofer, of Vienna, records coma and death in a drunkard following the ingestion of half a drachm. W. H. Lathrop details the case of a man previously healthy, but suffering from delirium tremens, who took sixty grains between 12 and 1 P.M., at 2.30 P.M. twenty grains more, and at 3 P.M., no effect being manifest, twenty grains more. His physicians then left him sleepless and complaining only of a slight paralysis of the lower extremities; and almost in a moment he was dead. Other cases might be quoted, but the above are sufficient to show that chloral may kill suddenly and unexpectedly.

An observation of Vulpian throws much light upon these sudden deaths. He found that galvanization of a divided vagus would cause in a chloralized animal not momentary, but permanent, arrest of respiration, if the centric end was selected, or permanent diastole of the heart if the distal part of the nerve was attacked. It is very probable that in a man under the influence of chloroform or of chloral, death may be precipitated by a slight peripheral inhibitory irritation.

**Toxicology.**—The earliest symptoms of hydrated chloral-poisoning is sleep, which in mild cases closely resembles natural sleep. The subject can readily be aroused from the lighter degrees of this, waking to full consciousness, but soon dropping off again when left quiet. The pulse is in this degree of action not affected, or is rendered a little slower; the pupil is contracted, but becomes normal so soon as the subject is awakened; the respiration is deep, full, and regular. When larger amounts are given, the sleep is much deeper, and may pass into profound coma; the respirations fall in number; the pulse at first is weakened and rendered slower, but later may become rapid and irregular; the temperature is reduced; the muscular system is relaxed, and both sensibility and reflex action are diminished. If a fatal dose has been taken, all these symptoms are intensified; with coma, intense muscular relaxation, weak, thready pulse, and a pupil contracted at first, but afterwards dilated, the victim gradually sinks into death, paralyzed and anesthetic. The immediate cause of death is usually a centric paralytic arrest of respiration; but in many cases there appears to be a simultaneous arrest of the cardiac action, and it is probable that fatal syncope may at times occur.

The minimum fatal dose of hydrated chloral is hardly established, but thirty grains have produced death. (See *Administration*.) In very many cases, however, recovery has occurred after the taking of several drachms; indeed, Eshleman has reported recovery after the ingestion of four hundred and sixty grains. There are no pathognomonic lesions found after death from chloral, but a dark, bloated countenance and other evidences of death from asphyxia have been noted; congestion of the meninges and substance of the brain and cord, and of the lungs, is commonly found. The blood is thought by Richardson to coagulate less firmly than when normal.

There is no satisfactory chemical antidote to chloral. The *treatment* is in general similar to that of opium-poisoning, consisting in the free use of internal and external stimulants, such as sinapisms, dry heat, frictions, flagellations, etc., to maintain the circulation, and of shaking, application of the dry electric brush, cold douches, etc., to keep up the respiration. In practising these measures it must be remembered, however, that the patient in chloral-poisoning is much more likely to die of exhaustion, and especially of cardiac failure, than in opium-poisoning, and that therefore those methods of arousing the nerve-centres which do not, like walking, require the expenditure of effort on the part of the patient are to be preferred. Artificial respiration should always be resorted to before natural respiration altogether fails, and Clemens has found that animals asphyxiated by chloral may often be at once aroused by the inhalation of oxygen. Atropine and strychnine are important remedies. B. W. Stone reports recovery from four hundred and twenty-five grains of chloral after the hypodermic use of one-fifth of a grain of strychnine in divided doses. Digitalis may be given to sustain the heart. I. M. Booth reports a case of recovery after about one hundred and ten grains of chloral under the use of tincture of belladonna. Lauder Brunton has shown that if the bodily temperature be maintained artificially animals survive doses of chloral usually fatal, and in human chloral-poisoning the bodily warmth should be maintained by the use of dry external heat, hot blankets, hot baths, and other devices.

While some affections have been erroneously attributed to *chronic chloral-poisoning*, there seems to be no doubt that its long-continued use often does produce serious symptoms.

The cases are divisible into two or three groups, which are, however, really artificial, as is shown by the occurrence of cases belonging to two or even three of the groups. In the first group the respiration is chiefly affected. The dyspnoea may be slight, and may be felt at times, as after exertion or after meals; but it may be constant and alarming. Cases of this character are reported by Jastrowitz, by Schule, and by Ludwig Kirn. In one instance (N. R. Smith), death from bronchial effusion is believed to have been caused by chloral. Kirn affirms that in some cases mental disturbance with hallucinations occurs.

In the second group of cases, eruptions of the skin are the chief manifestations of the toxemia. These vary in intensity from the occasional appearance of transient red blotches on the face or neck to an intense, even livid, erythematous redness of the face. In other instances there is marked erythema (Schule), occurring first in spots upon the face, but extending downward to the trunk, becoming more and more general, and showing a marked tendency to follow the nerve-trunks. This erythema is seemingly due to vaso-motor weakness, and consequently is allied to other more urgent symptoms seen in chloral toxemia. Sometimes it invades the mucous membranes, which become red, swollen, and oedematous; and if the glands are involved, as in a case reported by Chapman, the result may be serious. A deeper implication of the vaso-motor and cardiac nervous system was probably the cause of the general oedema, profound weakness, and failure of heart-action in the case recorded by N. R. Smith and possibly also of the desquamation of the cuticle and ulcerations about the nails noted in some of his cases by the same physician.



In the third group of cases, petechiæ, ecchymoses, ulcerations, and even high fever and other pyemic symptoms, are asserted to have been produced by the continuous use of chloral. It seems to us, however, very doubtful whether the drug really was the cause of the symptoms which have been recorded by Crichton Brown, by Monkton, and by Kirn.

The habitual use of chloral as a narcotic has been indulged in, it is asserted, to a considerable extent, and George F. Elliott reports symptoms like those of *delirium tremens* as following the withdrawal of the accustomed draughts.

### SULPHONES.

The group of hypnotics known as the sulphones which were discovered by E. Baumann in 1866, include a number of compounds in which the hydrogen atoms of methane are replaced by alkylsulphonic radicals. The two most employed in this country are the so-called *sulphonal* (diethylsulfonedimethylmethane), and *trional*, (diethylsulphonemethylethylmethane). The original statement of Baumann and Kast that the hypnotic powers of these drugs is in direct relation to the number of ethyl radicals in their chemical make up has been confirmed by Diehl.

Sulphonal and trional are both of them colorless crystalline powders; the former is practically tasteless but trional has a slightly bitter flavor. Sulphonal is practically insoluble in cold water, but sparingly soluble in alcohol and in ether. Trional is also almost insoluble in water—requiring nearly 200 times its weight of water to dissolve it—but is readily soluble in both alcohol and ether.

#### Official Preparations :

Sulphonmethanum [Sulphonal] .....	30 to 45 grains (2-3 Gm.).
Sulphonethylmethanum [Trional] .....	10 to 30 grains (0.6-2 Gm.).

*Absorption and Elimination.*—Both of these drugs, owing to their slight solubility, are absorbed with great slowness, but of the two sulphonal is distinctly the slower in its action, requiring sometimes two hours for the manifestation of its effect. The elimination likewise takes place very slowly so that, after the use of sulphonal, drowsiness is frequently manifested the next day. When taken in large amount they escape to some extent through the kidney unchanged, but the greater portion is converted into an organic sulphur compound, which, according to the researches of W. J. Smith (confirmed by Baumann and Salkowski), is probably *ethyl-sulphonic acid*.

**Physiological Action.**—The sulphones as far as we know have very little effect upon the general system, the action being limited almost solely to depression of the brain. There is some evidence of a slight stimulant influence upon the spinal cord. The effects upon the circulation are practically nil.

In the frog, the dog, and the rabbit the sulphones produce sleep, which, if the dose be sufficiently large, deepens into coma, and is accompanied by paresis, tremors, and convulsions. Knoblauch affirms that not infrequently the loss of power in the

hind legs precedes sleep, and that weakness and ataxia are prominent symptoms after large doses. The convulsions, which are said to be epileptic, are produced by very large toxic doses only.

According to Haenel, the rate of the mental function is distinctly lessened by trional and continues slow for some time after the sleep period. If it be true, as asserted by Egasse, that in animals trional sleep is attended by increase in the activity of the reflexes, it probably stimulates the spinal cord. According to Shick sulphonal usually lessens spinal activity, by stimulation of Setschenow's centre, although in some of his experiments the reflexes were increased. The same author reports that it has no influence upon the motor or sensory nerves, nor upon the muscles.

Kast found that there is neither microscopic nor spectroscopic blood changes in animals acutely poisoned by sulphonal.

According to Kast, the blood-pressure is not altered by doses which produce sleep, and the rise of arterial pressure noticed by Shick in non-curarized animals may have been produced by failure of respiration.

Kronfeld, as the result of sphygmomanometrical studies, affirms that the blood-pressure is always lowered during sleep caused by trional, the fall being due, in his belief, to depression of the vaso-motor centres.

**Therapeutics.**—The sulphones are valuable hypnotics in nervous *insomnias* but have little or no analgesic effects. Of the two here described trional is ordinarily the preferable, being more prompt and certain in its effect as well as less liable to cause toxic manifestations from prolonged use. Sleep usually develops in from a half to one hour after the dose, in most cases gradually, but sometimes with abruptness. It is usually quiet, and not followed by any disagreeable after-effects, although sometimes mental confusion and lassitude remain during the following day; these after-results being, in our experience, especially likely to occur in cases in which there is a distinct depression of the brain-nutrition. Where the sleeplessness is due to pain, the sulphones are usually not serviceable; but in the insomnia of insanity it often acts well. Later experience, however, does not seem to carry out the original assertion of Kast, that sulphonal is especially useful in cases of insomnia from cardiac diseases. In such affections it appears to be not only an uncertain, but even a dangerous drug, inferior to chloral.\* At present this disagreeable action of the drug does not seem to be explainable by any influence exerted upon the heart. It is possible that it is due to irritation of already congested kidneys.

Sulphonal has been used with asserted good results in *epilepsy*, *hiccough*, *chorea*, and *nocturnal cramps*; according to E. Andrews, it is very effective against the *spasm* of *fractures*. It has also been commended as a sexual sedative in *chordee* and *spermatorrhæa*. In our own practice, sulphonal given an hour after meals has seemed to have value as an intestinal antiseptic. It is asserted that it is a very useful remedy in colliquative *night-sweats*.

**Administration.**—The sulphones are absorbed with difficulty, and should always be administered in fine powder diffused in water or milk, or enclosed in capsules. We have seen compressed pills of

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\* See Joachiam (*Therap. Monatsh.*, iii.); also Schmey (*Ibid.*, 1888, ii.),

sulphonal pass through the body unchanged, and have no doubt that the reported great slowness or even failure of action has often depended on improper methods of administration. It should be an invariable rule, when sulphonal is given continuously, to interrupt its use for at least four days every two weeks so as to allow the system to clear itself; and the urine should be watched and the first sign of a pinkish hue be the immediate order for the withdrawal of the drug. Also attention should be paid to having a daily free evacuation of the bowels.

**Toxicology.**—Although occasionally even the single dose of sulphonal produces nausea (even severe gastric pain: Dauthville), languor, headache, depression, or pronounced mental disturbance, poisoning from a single dose of either of these drugs is very rare, probably on account of the slowness of absorption. The statement sometimes made, however, that the single dose is incapable of taking life is untrue at least for sulphonal.

Pettitt states he has seen coma ending in death produced in a woman by two grammes of sulphonal. In a case recorded by G. Hoppe-Seyler and Ritter fifty grammes produced death in seventy hours, the symptoms having been coma, cyanosis, and high fever. The expired air had the odor of mercaptan, and the urine contained unaltered sulphonal. Pronounced fatty necrosis of the intestinal and renal epithelium, fatty degeneration of the heart, and broncho-pneumonia were found in the body. The broncho-pneumonia was believed by Hoppe-Seyler to be the result of the aspiration of the contents of the mouth and gullet, due to the insensibility of the epiglottis.

In one case recovery occurred after one hundred and twenty grains of sulphonal, although there were complete abolition of the reflexes and loss of the radial pulse.\* E. Neisser has recorded a case in which one hundred grammes caused a profound sleep lasting ninety hours, a fall of bodily temperature to 96° F., and a symmetrical minutely papulous eruption upon the hands, but no great disturbance of the heart or breathing or of the reflexes; after recovery there was a marked ataxia of speech and movement which disappeared in a week.

Sixty grains of trional have produced hematuria (Berger), but 120 grains have been recovered from with almost no symptoms (Collatz). Wightwick and Rolleston report a case in which 120 grains caused dilated pupils, loss of reflexes and cardiac depression

On the other hand serious and even fatal *chronic poisoning* from the prolonged use of these remedies is unfortunately not rare. The condition is more common from sulphonal, but trional has in several instances given rise to similar symptoms. The mortality in chronic sulphonal-poisoning has been extremely high.

Although prodromic symptoms probably always usher in *chronic sulphonal-poisoning*, they are so slight and so lacking in anything characteristic that in a large majority of cases the condition appears to develop abruptly, and usually, notwithstanding the suspension of the remedy, continues to the fatal issue, death occurring in about seventy-five per cent. of the cases. The first manifestations are increasing lassitude and weakness, nausea, and gastro-intestinal

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\* See *B. M. J.*, 1899, ii. 8.



disturbance as shown by diarrhœa or constipation. Ordinarily the first symptom noted is the pink coloration of the urine, which deepens until the fluid becomes of a dark red color, staining the linen upon which it falls. Usually this coloration of the urine is soon followed by obstinate constipation, violent vomiting, spasm of the abdominal muscles, and tenderness upon pressure in the region of the liver and stomach. At the same time there develop insomnia, ataxia, suppression of perspiration, paresis of the upper extremities or of irregular groups of muscles, pronounced weakness of the legs, loss of the patellar and other reflexes, paresthesia, various forms of skin eruptions, muscular spasms, and finally a condition of profound collapse, with highly acid, albuminous, hemorrhagic, or suppressed urine, ending in death. After death, widespread fatty degeneration, involving in some cases the heart, but especially affecting the liver and kidney, has been found. Erbslöh has reported multiple peripheral neuritis from the prolonged use of sulphonal.

In some cases the renal changes have been confined to a glomerular or cortical nephritis,\* with or without hemorrhage; in other instances the destruction of the kidney has been more complete. The most characteristic symptom is the appearance of hematoporphyrin in the urine; its recognition is best made with the spectroscope.

The symptoms caused by trional are practically the same as those just described although the premonitory manifestations are usually more marked. Hart has reported double wrist-drop, probably due to peripheral neuritis.

It has been shown by Salkowski (confirmed by Kast) that ethyl-sulphonic acid is not poisonous, and hematoporphyrin appears also to be free from toxic properties; so that the symptoms of chronic poisoning are probably due to an accumulation of the sulphone in the system, and are of largely primary and not of secondary character, though some of them may be in fact uremic. The explanation of the occurrence of hematoporphyrinuria is at present very difficult; † frequently it does not come on until several days after the ingestion of the last dose. In a fatal case of acute poisoning reported by Hoppe-Seyler and Ritter it was not present. As has been demonstrated by Garrod and Hopkins, the urine of patients taking sulphonal does not ordinarily contain more hematoporphyrin than is often seen in health. It is generally thought the hematoporphyrin is a decomposition product of hematin, and Stokvis believes that the hematoporphyrinuria is due to the absorption of altered blood from hemorrhages which have been produced in the mucous membrane of the stomach and intestines by sulphonal,—an explanation which is rejected by Kast and Weiss, and also by Garrod and Hopkins, for apparently sufficient reasons. The observations of Garrod and Hopkins, that the increase of urinary hematoporphyrin is not accompanied by a corresponding increase in the excretion of iron, and the fact that in the cases recorded by Percy Smith there was no lessening in the number of the red blood-corpuscles nor of the hemoglobin, lend probability to the assertion of Quinke (confirmed by Herting), that the coloring-matter of the urine is not in reality hematoporphyrin, differing from it in its spectroscopic

\* A. E. Taylor and Joseph Sailer (*Contributions William Pepper Lab.*, Philadelphia, 1900, cxx.) found that the degenerated cells of the liver, spleen, lymphatics, and kidney were loaded with green pigment, while the blood-serum contained hematoporphyrin.

† In an elaborate research upon rabbits, Neubauer (*A. E. P. P.*, 1900, Bd. xliii.) attempted unsuccessfully to determine how the hematoporphyrin is produced by sulphonal. In agreement with Kast and Weiss, he was unable to produce hematoporphyrin by digesting the normal organs of the rabbit with sulphonal.

lines. Franz Müller, however, found in a case of sulphonal-poisoning which recovered that the hemoglobin fell during the period of red urine to forty-five per cent., returning afterwards to eighty-five per cent.; while Hoppe-Seyler believes that the anatomical changes in sulphonal-poisoning are really secondary to the destruction of the red blood-disks.

In the *treatment* of chronic sulphone-poisoning the most important measure is to see that the bowels are thoroughly opened and cleaned of any undissolved drug which may be lying there and by slow absorption making the patient's condition continually more hopeless. For this purpose heroic measures are often necessary and vital time should not be lost experimenting with the milder cathartics. After this the poison should be diluted and elimination encouraged by the free use of water. This may best be given by hypodermoclysis of physiological salt solution as well as by the ingestion of water by mouth. The use of the alkaline carbonates, as suggested by Müller, is probably also of service.\* For the heart-failure and other symptoms the appropriate drugs should be administered, but they usually have very little effect.

### PARALDEHYDE.

This substance, which is a polymer of acetaldehyde, occurs as a colorless liquid, with a strong and disagreeable odor and a burning taste. It is soluble in 8 parts of cool water, less soluble in warm water, and mixes in any proportions with alcohol or ether.

Paraldehydum.....  $\frac{1}{2}$  to 1 fluidrachm (2-4 C.c.).

*Local Action.*—Paraldehyde is locally irritant, and is likely, when taken in large doses, to disturb the stomach, or at least to give rise to disagreeable eructations.

*Absorption and Elimination.*—Absorption of paraldehyde commences at once, and its action is usually manifested in a few minutes. Its elimination begins promptly, but is carried on slowly, so that the breath frequently reeks of it for hours after the patient has awakened. Its chief channel of escape is probably through the respiratory organs, but it has been found in the urine by Gordon and Raimann, and Raimann also believes that it escapes to some extent with the perspiration. It appears not to be destroyed in the system.

*Physiological Action.*—According to the physiological studies of Cervello, Prévost, and Gordon, the injection of from one-half to one drachm of paraldehyde produces in the rabbit and dog loss of sensibility, and in a very short time deep sleep with general muscular relaxation, some slowing of the breathing and of the rapidity of the heart, without, however, distinct lowering of the blood-pressure. After very large doses reflex excitability is abolished, and death takes place through respiratory paralysis, the cardiac action and blood-pressure long resisting the action of the drug. In man paraldehyde

\* Alkaline waters, however, in Pollitz's case (*Vierteljahr. f. Gerichtl. Med.*, 1898, v.) apparently failed to do any good.

produces a deep sleep, with, if the dose have been large enough, loss of reflex activity, some slowing of the respiration and pulse-rate, and slight fall in the temperature. The symptoms usually pass off without disagreeable after-effects, but after very large doses there are sometimes malaise, headache, giddiness, nausea, or even vomiting. Usually there is some diuretic action.

*Nervous System.*—Paraldehyde\* probably produces sleep by a direct action upon the cerebral cells. Bokai and Barcsi have found that there is marked relaxation of the cerebral blood-vessels, but this is probably the result, not the cause, of the arrest of brain function. The characteristic effect of the drug upon muscular action is depression, which is probably of spinal origin, though this has not been absolutely proved. Bokai and Barcsi affirm that after small doses there is a period of heightened reflexes.

*Circulation.*—Upon the circulation paraldehyde has very little influence, nor is the blood itself affected except by the very largest doses. According to Henoque, intravenous injections of paraldehyde in the animal are followed by disappearance of the absorption-band in the yellow-green of the oxyhemoglobin spectrum.

*Nutrition.*—According to Dockendorff, the elimination of nitrogen and phosphorus is somewhat lessened by paraldehyde, and in cases of chronic poisoning in man the elimination of phosphates has been found to be very low. Hemoglobinuria has been noticed in the horse, but not in other animals poisoned with paraldehyde.

*Therapeutics.*—Paraldehyde is a very useful hypnotic in the numerous cases of mild insomnia, such as is seen in neurasthenia, and is also used as an adjuvant to other remedies in *delirium tremens*, *insanity*, and the more serious forms of morbid wakefulness not dependent upon pain. It is one of the most prompt, as well as safe, of the somnificants.

*Toxicology.*—Very large doses of paraldehyde have been taken without fatal results, although death is alleged to have been produced by four ounces (Drage). In one case reported by Raimann, nearly eight hundred grains produced simply deep sleep lasting nineteen hours, without evil result. Probst reports one case in which nine hundred grains gave sleep lasting twenty-two hours, without serious symptoms; and another in which nearly five ounces of paraldehyde, taken within thirty-six hours, produced profound coma, marked lividity, excessive muscular relaxation and vomiting, slight fall of temperature, without pronounced depression either of the heart's action or of the blood-pressure, and without complete loss of the reflexes. The urine at first was in no way abnormal; later it contained acetone. On the second day mental aberration appeared and continued, and on the fifth day distinct tremors appeared: by the seventh day the case was convalescent. Although chronic poisoning has frequently been produced by paraldehyde, we know of no recorded

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\* Cappelli and Brugia have also noted lessening in the size of the brain under the influence of paraldehyde, in a man suffering from defect of the skull.



fatal case. Disturbances of the digestion are common. More characteristic is a psychic disturbance somewhat resembling delirium tremens and in many cases associated with tremors and muscular weakness. These symptoms usually subside with the cessation of the taking of the drug. In one case thirty-five grammes were taken daily for a year. In a second case five grammes were taken daily for thirteen years, without the production of any symptoms.\* In the experiments of Bokai and Baresi it was found possible to produce in the animal, by the continued use of paraldehyde, fatty degeneration of the liver and of the heart-muscle, but no such result has been noted in man. In some cases nasal ulcers, skin eruptions, and various vaso-motor disturbances are said to have been produced by the long administration of the drug.

**ETHYL CARBAMATE.**—The ethyl ester of carbamic acid, commonly called *urethane*, occurs in the form of odorless columnar crystals or scales, of a cooling, saline taste, soluble in less than one part of water. It was originally proposed by Schmiedeberg as an hypnotic which acts directly upon the cerebral cortex, depresses the motor side of the spinal cord, but has very little influence upon the circulation, the arterial pressure remaining normal even during deep narcosis. Clinical experience has shown that urethane is safe but somewhat uncertain in its action, and that it may be used, sometimes with satisfactory results, as an hypnotic and also as an anti-convulsant in *puerperal* and other serious *eclampsia* as well as in *tetanus*.

*Æthylis Carbamas* [Urethane].....15 to 30 grains (1-2 Gm.).

**CHLORALFORMAMIDE.**—Under the name of *chloralformamide*, a compound of anhydrous chloral and formamide has been used as an hypnotic and has been made official in the U. S. Pharmacopœia. It is a slightly bitter crystalline substance, soluble in 18.7 parts of water and 1.3 parts of strong alcohol. It is decomposed by hot water, but its solution in cold water is moderately permanent; it is rapidly decomposed by alkalies. In the lower animals chloralformamide produces lethargy, narcosis, sleep, and, finally, if it has been taken in sufficient amount, death from failure of respiration. According to Langgaard in the rabbit the sleep is accompanied by pronounced decrease in the amount of air drawn in and out of the lungs and pronounced lessening of the blood-pressure. These results, however, are scarcely in accordance with those of other observers. Otto Halasz found the blood-pressure very slightly affected. Von Mering and Zuntz have shown that the fall in the air movements of respiration obtained by Langgaard was not greater than that which results from sleep, and also obtained deep sleep and even complete anesthesia in the rabbit without fall of the arterial pressure.

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\* See *V. A. S.*, 1887, xiv., and *Cb. N.*, 1900, p. 139.

In a series of experiments made by David Cerna and H. C. Wood in the laboratory of the University, it was found that the influence of chloralformamide upon the circulation is very feeble, only the largest toxic dose lowering the arterial pressure at all. In the dog the respirations were always enormously hurried by the drug, although no experiments were made to determine the absolute amount of air moved. The action of the drug upon the spinal cord was also very feeble, and no perceptible influence was shown upon the nerves and muscles; but the effect upon the cerebral cortex was very pronounced.

Chloralformamidum [Chloralamid] . . . . . 20 to 40 grains (1.3–2.7 Gm.).

**Therapeutics.**—Chloralformamide is a rather slowly acting and uncertain hypnotic, which usually does not cause any unpleasant after-effects, but sometimes produces confusion, giddiness, and headache. It has been especially recommended by Hagemann and Hüfler for the relief of cardiac *asthma*. Our knowledge of its physiological action seems to show that the assertions of various clinicians, that it is better borne than hydrated chloral in cases where there is cardiac weakness, have a foundation in fact. It should be given in watery solutions or capsules half an hour before the expected time of sleep.

**AMYLENE CHLORAL.** *Dormiol.*—This drug, formed by the union of chloral and amylene hydrate, is a colorless, oily liquid with a camphor-like odor, insoluble in water. There is much recorded clinical evidence as to its value in insomnia which is not dependent upon the existence of pain. It has been largely employed in insane asylums, and it is asserted that it has no disagreeable after-effects; that it is not depressant to the heart, and may be used in cardiac insomnia; and that when continuously exhibited it does not produce chronic poisoning. Its action is prompt, but somewhat fugacious, and patients rapidly become accustomed to its use. Dose, from ten grains to one drachm (0.6–4 Gm.) in capsules or dropped in cold water.

**HEDONAL** (*Methyl-propyl-carbinol-urethane*).—This occurs in colorless crystals, sparingly soluble in cold water, of a disagreeable somewhat menthol-like taste, which are believed to split up in the system into carbon dioxide, ammonia, and urea. It has been brought forward as an hypnotic, which in severe cases of *insomnia* or when the patient is kept awake by pain, is of little service, but is valuable in mild cases on account of having no disagreeable after-effects. No cases of poisoning by it have been reported, and so far its prolonged use has not been followed by disagreeable symptoms. It is not known to have any influence upon the circulation, and, resembling triol in its action, has been especially commended as an alternative to that drug. Probably owing to the formation of urea, it sometimes acts as a diuretic, and, according to De Moor, this action is much increased by its administration in solution. Dose, from fifteen to forty-five grains (1–3 Gm.), preferably administered in capsules half an hour before the desired effect.

**ISOPRAL** (*Trichlorisopropylalkohol*).—This substance, readily soluble in water, alcohol, or ether, has a camphor-like odor and aromatic taste. According to Impens, it is readily absorbed through the skin, the subcutaneous tissue, and the digestive tract, its effects when taken internally being manifested in from three to five minutes. The claim of Impens that it is only half as toxic in proportion to its somnifacient power as hydrated chloral has been contradicted by Hatcher, who finds that while it is somewhat more powerful it is also more toxic than hydrated chloral and is a powerful depressant to both the circulation and respiration.

**VERONAL** (*Di-ethyl-malonyl-urea*).—This drug occurs in odorless, colorless, slightly bitter crystals, soluble in one hundred and forty-five parts of water at 68° F.

Originally brought forward by E. Fischer and J. von Mering as an hypnotic, veronal has been tested by various clinicians in all forms of insomnia, with reports which are very favorable. It has been found by Mendel and Kron and by Weber\* to be especially valuable in the treatment of insomnia with motor excitement or active hallucinations, also in depressive insanity; contrary to the statements of some clinicians, Mendel and Kron deny its value as an antineuralgic. Concerning its general physiological action we have little knowledge, but C. Trautmann affirms as the result of experimental studies that it lessens nitrogenous elimination. Various authorities assert that it leaves no after-effects; but Jolly, Rosenfeld, and Würth have noticed after its taking, malaise, headache and giddiness, and even disturbances of speech, chiefly when it has been given in very large doses. Fatal cases of poisoning by veronal have been reported by Germann (200 grains) and Farncomb.

Originally recommended in doses of half a gramme, veronal has been given practically up to one and a half grammes, but has been reported by various observers as efficient in much less amount; so that at present from ten to fifteen grains (0.6–1 Gm.) may be considered as its dose.†

**CHLORALOSE** occurs in small crystals, having a very bitter and disagreeable but not acrid taste. It is freely soluble in hot water, slightly so in cold water. It was first brought forward as a remedial agent by Hanriot and Richet, who state that five grammes of it will produce in a dog of ten kilogrammes' weight symptoms of intoxication followed by a most profound sleep in which all sensibility is lost, although the reflex activities are greater than normal; that upon the circulation it has but little power, the arterial pressure, even when there is profound unconsciousness, being scarcely affected; that during the unconsciousness not only is the motor side of the spinal cord more active than normal, but the cerebral cortex is excessively excitable, the animals experimented upon offering a strong contrast with chloralized dogs, in which the cerebral cortex is almost devoid of responding power. The statements of its discoverers, that, taken in doses of five grains, it would produce in man a profound sleep lasting for many hours, and not followed by unpleasant after-effects, have not been sustained. Its action is very variable; the dose of ten grains will in many cases produce no effect, and yet in other cases has caused complete unconsciousness with marked cyanosis and slowing of the pulse. Its therapeutic influence has frequently been attended by very unpleasant symptoms, such as tremors, partial or general paralysis, great slowing of the pulse and cardiac depression, involuntary discharge of urine during sleep, excessive vomiting, and delirious intoxication. In our experience, although occasionally useful, the drug has not proved generally satisfactory. Dose, from five to ten grains (0.3–0.6 Gm.).‡

**CHLORETONE**, *Acetone-chloroform*, or *Trichlor Tertiary Butyl Alcohol*, is a white crystalline compound with a camphoraceous odor; very soluble in strong alcohol and ether, soluble to the extent of about one per cent. in cold, more soluble in boiling, water.§

**Physiological Action.**—In proper dose chloretone causes in the lower animals a profound sleep, with complete and prolonged anesthesia, without marked effect upon the respiration or blood-pressure. This condition may be continued as long as four days, and the animal wake unharmed; but if the dose has been

\* For references, see *D. W. M.*, 1903, pp. 608, 726.

† See *S. Jb.*, Bd. cclxxviii., cclxxix., for abstracts of the literature to date; also *Ther. Gaz.*, 1903.

‡ See *Brit. Med. Journ.*, 1893, ii. For cases of unpleasant action, see *Schmidt's Jahrb.*, ccxiv.; also *Revue Neurolog.*, 1894, ii.

§ Chloretone was discovered by Willgerodt in 1881, and suggested as a substitute for chloral by him in 1884. In 1891 John J. Abel began to experiment with it, and in 1894 demonstrated its usefulness as a practical hypnotic and anesthetic for the physiologist (see *Science*, January, 1895).

Abel states that Faust has found that urethane and chloretone rubbed together make a fluid. The physiological properties of this substance do not seem to have been investigated.



sufficient, after several days of sleep death occurs from asphyxia. According to E. M. Houghton and T. B. Aldrich, applied locally to the frog's heart, it slows the rate and produces a more complete systole, and has no action upon the blood itself. Locally applied it is a sensory nerve paralyzant. Houghton and Aldrich having failed to detect it, acetone, or chloroform in any of the excretions of the poisoned animal, believe that it undergoes decomposition in the body.

**Therapeutics.**—Chloretone has proven to be a very uncertain hypnotic\* and to-day is comparatively little employed except as a local remedy. It appears to possess both antiseptic and anesthetic powers and is applied to foul, irritable ulcers and wounds. It has also been employed in doses of from five to eight grains in vomiting, gastric cancer, and other painful local conditions of the stomach. As an hypnotic it has been used in ordinary *insomnia*, *delirium tremens*, and various forms of *insanity*, but is uncertain in its action. According to Wharton Sinkler, it is useful in *epilepsy*, and especially in *petit mal*, in doses of from three to five grains (0.2–0.3 Gm.), three times a day.

We know of no deaths reported from chloretone; one hundred and twenty grains taken during twenty-four hours (W. M. Donald) caused profound sleep lasting for six days, without any untoward symptoms except gastric irritability. The pulse ranged from 85 to 104, and the bodily temperature fell to 96° F.

The dose of chloretone has been set down from twelve to fifteen grains (0.8–1 Gm.), but we have exhibited thirty grains in the twelve hours without the production of any symptoms whatever; and Wade, who has used the drug largely, gave the average dose as from thirty-five to fifty grains.

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\* According to Impens (A. I. P. T., 1901, viii. 77), chloretone is a much more dangerous hypnotic than chloral, the ratio of the somnifacient to the fatal dose being only as 1: 1.7.

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## FAMILY IV.—DELIRIFACIENTS.

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IN the present group are considered medicines whose preparations, when taken into the system, cause marked dilatation of the pupil and act upon the cerebral nerve-cells so as to produce delirium.

Most of these belong to the Solanaceæ, or nightshade family. This is one of the most remarkable groups of plants in all the vegetable kingdom; it yields such common vegetables as the potato and tomato, as well as tobacco and a number of other powerful poisons. The most important plants, from a therapeutic standpoint, belonging to this family are the *Atropa belladonna*, the *Datura stramonium*, the *Scopola carniolica* and the *Hyoscyamus niger*. From these and allied plants a large number of alkaloids have been isolated. Many of these which have been thought to be pure principles have been shown subsequently to be simply mixtures of previously discovered bases. The most important alkaloids found in these plants are atropine, hyoscyamine\* and hyoscyne.

*Atropa belladonna* (deadly nightshade) is an herbaceous perennial, native to Europe. The leaves and root are both official. The leaves (*Belladonnæ Folia*) are four to five inches long and two to four inches broad, ovate, with entire margin. The root (*Belladonnæ Radix*) occurs in brown wrinkled pieces about the thickness and length of the finger, somewhat tapering. *Belladonna* leaves should contain not less than 0.3 per cent. of mydriatic alkaloids, of which the most important are atropine and hyoscyamine. The root should contain 0.45 per cent. of the same alkaloids.

*Stramonium* is the leaves of *Datura stramonium*, or jimson-weed, a common plant growing in waste places in many parts of the United States. The plant is characterized by the vivid green color of its leaves, white to purplish flowers and a peculiar thorny fruit which gives to it the name of "thorn apple." The leaves are from four to five inches long and deeply toothed. The alkaloid *daturine*, which has been described as its active principle, seems to be a mixture of atropine and hyoscyamine, and is present in the proportion of 0.25 per cent.

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\* Atropine and hyoscyamine are isomeric compounds. They may be easily distinguished however by their relations to polarized light. Whereas hyoscyamine rotates polarized light to the left, atropine is without rotatory power. According to Amenomiya (*Archiv der Pharmacie*, 1902, 240, p. 498) atropine is, however, a mixture of a lævo- and a dextro-rotatory substance resulting in an optically inert body. Cushny (*J. P.*, 1903, vol. 30, p. 177) found that hyoscyamine qualitatively acted like atropine but that it was twice as powerful in its effects upon certain nerve terminals, as the vagi, glands and the pupil, and was less active as a convulsant. He reasoned that the lævo-hyoscyamine affected chiefly the peripheral nerves and that the dextro-hyoscyamine affected more powerfully the central nervous system. A few experiments made with the dextro-hyoscyamine by Amenomiya seemed to confirm this deduction, this substance being only one-tenth as active in its effects upon the peripheral nerves as the lævo-hyoscyamine. There appear similarly two-varieties of hyoscyne (see p. 108). For all practical purposes hyoscyamine and atropine may probably be properly considered as identical in their effects. (See Shaw, Richter, Ringer and H. C. Wood, Jr.)



*Hyoscyamus niger*, or henbane, is a European plant, of which the leaves are official. These somewhat resemble the leaves of the stramonium but are larger. They contain 0.08 per cent. of alkaloids, mostly hyoscyamine, with some hyoscyne; the latter alkaloid is generally believed to somewhat modify the dominant action of hyoscyamine.

Scopola is a rhizome of *Scopola carniolica*, a European plant, very similar to, if not identical with *Scopola japonica*, or Japanese belladonna. It contains 0.5 per cent. of total alkaloids, chiefly hyoscyamine, with some hyoscyne and atropine.

#### Official Preparations :

Extractum Belladonnæ Foliorum.....	$\frac{1}{2}$ to $\frac{1}{2}$ grain (0.008–0.031 Gm.).
Tinctura Belladonnæ Foliorum (10 per cent.) .....	10 to 30 minims (0.6–2.0 C.c.).
Fluidextractum Belladonnæ Radicis.....	1 to 2 minims (0.06–0.12 C.c.).
Linimentum Belladonnæ (5 per cent. camphor in fluidextract) .....	External use.
Emplastrum Belladonnæ.....	External use.
Extractum Stramonii.....	$\frac{1}{2}$ to $\frac{1}{2}$ grain (0.008–0.031 Gm.).
Fluidextractum Stramonii.....	1 to 2 minims (0.06–0.12 C.c.).
Tinctura Stramonii (10 per cent.).....	10 to 30 minims (0.6–2.0 C.c.).
Unguentum Stramonii.....	External use.
Extractum Hyoscyami.....	1 to 3 grains (0.06–0.19 Gm.).
Fluidextractum Hyoscyami.....	3 to 5 minims (0.2–0.3 C.c.).
Tinctura Hyoscyami (10 per cent.).....	$\frac{1}{2}$ to 2 fluidrachms (2–8 C.c.).
Extractum Scopolæ.....	$\frac{1}{2}$ to $\frac{1}{2}$ grain (0.008–0.016 Gm.).
Fluidextractum Scopolæ.....	1 to 2 minims (0.06–0.12 C.c.).

The following alkaloidal preparations are also recognized:

Atropina.....	$\frac{1}{200}$ to $\frac{1}{60}$ grain (0.3–1.0 Milligm.).
Atropinæ Sulphas.....	$\frac{1}{200}$ to $\frac{1}{60}$ grain (0.3–1.0 Milligm.).
Oleatum Atropinæ (2 per cent.).....	External use.
Hyoscyaminæ Hydrobromidum.....	$\frac{1}{200}$ to $\frac{1}{60}$ grain (0.3–1.0 Milligm.).
Hyoscyaminæ Sulphas.....	$\frac{1}{200}$ to $\frac{1}{60}$ grain (0.3–1.0 Milligm.).

### ATROPINE.

Atropine occurs in silky prismatic and acicular, often aggregated, crystals, of a bitter, burning taste, without odor, practically insoluble in water, and therefore always used in the form of the sulphate. It is most abundant in the root, and, according to M. Lefort, in that of young plants.

**Physiological Action.**—*Local Action.*—*Elimination.*—Atropine is not irritant, but when locally applied in sufficient concentration is probably paralyzant to most of the higher forms of protoplasm, overpowering the capillary walls, the sensory and motor nerves, and even muscular and glandular cell-action. A. Zeller has found that a one-per-cent. solution of atropine brought in contact with the blood, outside of the body, checks the movements of the corpuscles.

Atropine is absorbed with great rapidity from the primæ viæ and slowly but certainly through the skin. It is eliminated in great part

or altogether unchanged, chemists having failed to find in any secretion the natural decomposition product, ecgonine, and Wiechowski having recovered, on an average, thirty-three per cent. of the injected atropine from the urine. It has been found in all the tissues of the poisoned individual, and S. Fubini and O. Bonanni have detected it in the milk, but it chiefly escapes by the kidneys; hence poisoning may often be diagnosed by dropping the urine of the patient in the eye of a cat or other domestic animal, when mydriasis will be produced.

Upon the lower animals belladonna to a great extent acts as upon man, although its influence is much less powerful in them, and very much larger doses are required.

In their sensitiveness to atropine animals differ very much, and, as a general rule, herbivora are less susceptible than carnivora. Thus, the rabbit may be fed for days entirely upon belladonna-leaves without injury, and many grains of atropine are necessary to kill it. Pigeons we have found will often recover after the hypodermic injection of two grains of atropine, and, according to Féré, 1.75 grammes taken by the mouth will not kill a hen of 2.9 kilogrammes' weight. A very curious fact, which we have repeatedly verified, is that the pupils in pigeons cannot be dilated by the use of belladonna. According to Richet, the monkey offers an extraordinary resistance to the action of atropine.

*Circulation.*—Atropine may cause a primary slowing of the pulse—very brief and only occasionally to be demonstrated—but the characteristic results of its administration are rapid pulse with a great rise in the arterial pressure. After large toxic doses the rise of pressure may be followed by a fall.

The increase in the pulse-rate is due to the paralysis of the peripheral terminations of the pneumogastric nerve, as is shown by the fact that electrical irritation of this nerve fails to slow the heart. The rise of pressure depends chiefly upon a stimulation of the vaso-motor centres and the increase in the rate of the heart, although there is some evidence to lead us to believe that the drug exercises a slight stimulant influence upon the cardiac muscle.

The primary fall of the pulse, in accordance with the experiments of Bezold and Bloebaum, is due to stimulation of the inhibitory cardiac centre; these observers having found that when atropine is injected into the carotid so as to reach the pneumogastric centres before the pneumogastric nerve-endings, there is instantaneously a great fall in the rate of the heart's beat. Of course, in the fully atropinized animal any effect of the drug upon the inhibitory centres is masked by the inability of the paralyzed vagi to carry impulses from the centre, and, in fact, only in especial cases is the primary slowing manifested.\*

The rise of pressure is due chiefly to stimulation of the vaso-motor centre as shown by the fact first demonstrated by Bezold and Bloebaum, and confirmed by H. C. Wood, that after section of the spinal cord the alkaloid is powerless to produce a rise of pressure. Further Bezold and Bloebaum have found that when a small dose of atropine is injected into the carotid artery,—that is, into the vaso-motor centres, there is an instantaneous rise of pressure.†

\* See *Stille's Therapeutics*, i. 725. Mitchell, Keen, and Morehouse found it in about one-third of the cases after large hypodermic injections, Da Costa in a large proportion (*Amer. Journ. Med. Sci.*, July, 1865), and Miss Mary Putnam in some cases (*New York Medical Record*, 1873).

† The evidence as to the effect of atropine upon the blood-vessels obtained by direct observation of the capillaries of a frog under the microscope on the whole favors the view of vascular contraction; but we believe the method of experimentation so fallacious as to be of little evidential value.

While it may be considered to be established that overwhelming doses of atropine act as a direct paralyzant to the heart-muscle, the question as to the effect of small doses has been much debated.

Probably very minute quantities exert a feeble, stimulating influence upon the mammalian heart; thus, Ramson discovered that atropine causes in the heart of the octopus excitation of the muscular fibre; O. Langendorff found that when the cut-off apex of the frog's heart was touched with a minute quantity of atropine it

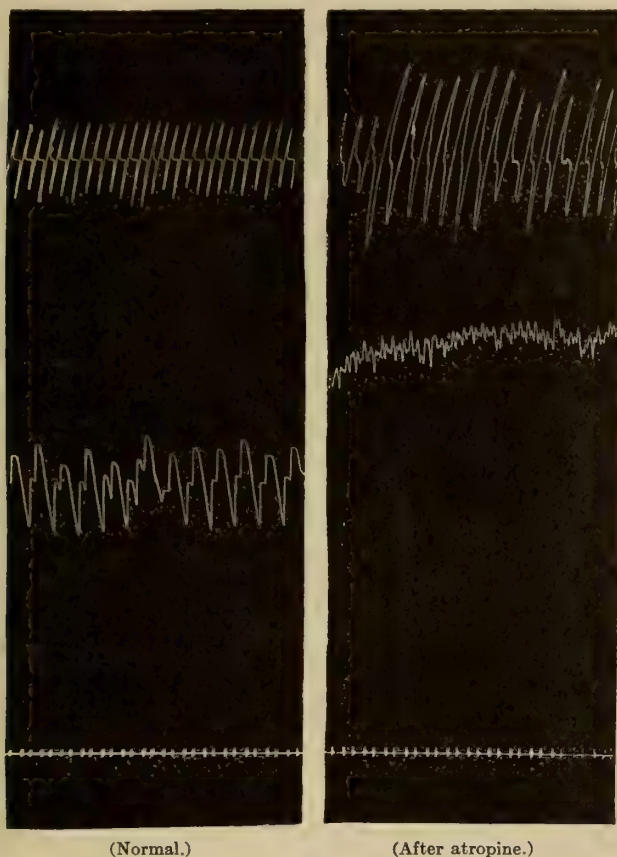


FIG. 7.—EFFECT OF ATROPINE ON THE PULSE AND RESPIRATION.

Atropine increases the rate of the pulse by paralyzing inhibition; it stimulates the vaso-motor centres, causing a rise of the blood-pressure. It also increases the respiration. Time marker indicates 1 second.

immediately commenced to beat;\* and G. Beyer noticed that the ventricles of the isolated terrapin's heart are stimulated by minute quantities of the alkaloid, although they are arrested in diastole by larger amounts. This action of the drug upon the heart-muscle is probably the cause of the increased pulse-rate which has been noted as occurring when atropine is given after division of the vagi, although it is possible that this increase is due to stimulation of the accelerators.†

\* The reports as to the action upon the rate of the frog's heart are somewhat at variance, Bowditch and Luciani having noted an increase, Gnauck a lessening, in the cardiac pulsations (*Verhandl. Physiolog. Gesellsch. zu Berlin*, 1881). H. Schapiro states that this variance is accounted for by the fact which he has discovered, that whereas at high temperature (15° C.) the pulsations are diminished, at low temperature (7° C.) they are increased.

† See *University Med. Magazine*, May, 1891.



The final fall of blood-pressure in atropine-poisoning is due to its depressing influence upon the heart-muscle and upon the muscles in the walls of the capillaries. The local application of the alkaloid to the web of the frog's foot is soon followed by a complete paralytic dilatation of the vessels; further, Bezold and Bloebaum have found that in atropine-poisoning the arterial muscular coats finally lose their irritability, but that, so long as they retain it, galvanic stimulation of a sympathetic nerve does not fail to induce contraction in the tributary vessels.

*Nervous System.*—The delirium which is so characteristic of atropine-poisoning shows that it has especial relations with the cerebral cortex. Albertoni finds that neither the single large dose nor the repeated continuous dose has any power in preventing the epileptic seizure resulting in dogs from the stimulation of the motor zone of the cortex: enormous toxic doses seem only to render the response slower and less vivid. The influence of atropine upon the psychomotor centres would, therefore, appear to be slight. It should be noted that atropine is not in a proper sense hypnotic, the stupor which it produces being due to an overwhelming of the cerebral cortical centres, and not being preceded by sleep.

Thomas R. Fraser discovered, in 1869, that if a frog receive an injection of about one-thousandth part of its weight of atropine, a condition of complete paralysis and obliteration of reflex action comes on after a time and lasts from two to four days, to be succeeded by a tetanoid stage with violent convulsions of spinal origin and excessive excitability of the reflex centres. The explanation of this peculiar sequence is not definitely proven. The objection to the theory of Fraser that the drug is a spinal stimulant and that the stimulation of the spinal cord is masked by a paralysis of the peripheral nerves is given below. The most satisfactory explanation as yet put forth appears to us to be that which is based upon the theory of the existence of a spinal inhibitory centre.

According to this theory the spinal cord has within it two functions, motion and inhibition, certain cells giving off motor impulses, certain nerve-fibres inhibiting these motor impulses. In the normal cord the motor cells are under continual inhibition; under the influence of atropine it is believed that both motor and inhibitory functions are paralyzed; hence the general paralysis. After a time, however, the motor cells recover themselves so as to be able to generate impulses freely, although the inhibitory function of the cord is still depressed, the effect being an apparently true spinal excitement, which is due to lack of inhibition, the motor cells being actually weak. At such a time a peripheral impulse reaching the motor cell, instead of giving rise to a simple reflex action, and then being inhibited, passes on and starts a series of reflex movements involving all the muscles and constituting a tetanic convulsion.\*

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\* The conjunction of excessive irritability with lack of power in motor cells is a common condition in hysteria and neurasthenia. The fact discovered by H. C. Wood, that choreic movements of the dog are increased by atropine and diminished by quinine,—an inhibitory stimulant,—fits very well with the theory of the text, and also with the further facts discovered by E. T. Reichert, that if a dog to which a supra-fatal dose of atropine has been given be kept alive by artificial respiration, choreic movements occur which are arrested by intravenous injections of quinine. It

In the frog atropine acts as a depressant to the peripheral endings of the motor nerves although it rarely leads to complete paralysis such as is seen after curare. This effect is not demonstrable in man through the systemic influence of the drug, but may be brought out by its local application in the neighborhood of the nerve terminals. Atropine appears also to exercise a depressant influence upon the sensory nerves although not so marked as on the motor trunks.

It was originally shown by S. Botkin that tying the vessels of a frog's leg so as to shut off access of atropine to the nerve, interferes with the paralyzant action of the drug in that leg, while in the unprotected leg the poisonous effects of the drug were seen; and that the nerves after death from atropine-poisoning have largely lost their power of responding to galvanic currents. Fraser confirmed this observation—as did also Meuriot and others—and believed that the cause of the primary paralysis noted by him was the effect of the drug upon the peripheral nerves. This conclusion however has been brought into question by Ringer and Murrell, who found that the protection of the nerve-trunks did not hasten a development of the tetanus and also that in some instances there was between the stage of paralysis and of excitement a stage of normal voluntary and reflex action.

The action of atropine upon the sensory nerves is similar to its influence upon the motor nerves, although less powerful. S. Botkin found that if in the atropinized frog the nerve of one leg had been protected from the poison by tying the artery, irritation of the foot of the non-protected leg at a time when that leg was completely paralyzed would cause spasm in the opposite limb whose motor nerve was protected; yet later in the poisoning, although irritation of the foot of the protected leg would cause movement in that leg, no irritation of the opposite poisoned foot was able to induce response, showing that at first the sensory nerve was intact in the paralyzed leg, but that it finally succumbed to the poison.

Meuriot found that if a frog be bound tightly around the body so as to interrupt the circulation, and then be poisoned by atropine in the front part of its body, at first irritations in any part will give rise to general spasms, but after a time in order to get any movements of the hind legs it is necessary to apply an irritant to them. Again, the hinder parts of a frog were so bound by ligatures as to cut off on the one side all communication except by the nerves, and on the other to leave free the nerve and the vessels. A large injection of atropine was then given, and followed by strychnine, when it was found that, while irritation of the atropinized leg had no effect, stimulation of the non-atropinized leg gave rise to general convulsions. It is plain, however, that the influence of atropine upon the sensory nerve is feeble; for, Botkin found that immersion of a sciatic nerve for some little time in a two-and a half-per-cent. solution of the alkaloid did not, in the strychnized frog, prevent the nerve transmitting the impulse, since irritation of the foot would produce general convulsions.

*Muscles.*—The voluntary muscles escape unscathed in atropine-poisoning. It is true that Lemattre has shown that the contractility of a striated muscle may be destroyed by soaking it in a very concentrated solution of the alkaloid; but long before any such action can take place in life the animal is killed; consequently after death from belladonna the contractility of the voluntary muscles is found unimpaired.

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would appear that choreic movements are the result of inhibitory weakness; that atropine, increasing inhibitory weakness, increases choreic movements; and that quinine, stimulating inhibition, decreases these movements; and that the two alkaloids, so far as inhibition is concerned, are directly antagonistic.

On the non-striated muscles the action of atropine is pronounced, but its exact nature is at present writing somewhat uncertain. It may, we believe, be considered proved that the toxic dose of atropine finally depresses all non-striated muscles; the original assertion of Bezold and Bloebaum, that this paralysis may become so complete that the strongest faradic currents are unable to cause movements either in the intestines, bladder, uterus, or ureters, being probably correct.

The uncertainty is as to the effects of small doses. P. Keuchel seems to have proved that by a certain dose of atropine a condition is reached in which, although the peristaltic movements of the intestines are active, galvanism of the splanchnic—the inhibitory nerves of the intestinal coats—fails to have effect. If this be true, atropine paralyzes the peripheral inhibitory intestinal apparatus precisely as it does that of the heart. I. Ott states that very minute doses of atropine prevent the production of peristalsis by salt placed upon the intestines, while large doses exaggerate the action of the salt. Admitting the correctness of the experiments of Ott and Keuchel, it is evident that atropine first stimulates the intestinal inhibitory nervous system and then paralyzes it. This, moreover, is corroborated by the fact that the smallest dose used by Keuchel was 0.075 grain, by Ott 0.015 grain, both observers experimenting on the rabbit. When Ott used 0.45 grain he got the same result as did Keuchel.

*Respiration.*—The medicinal dose of atropine ordinarily has no apparent effect upon the respiration; but both in man and in the lower animals the large dose usually, though not always, accelerates the breathing, through a direct influence on the respiratory centres.

Researches upon the effect of atropine upon the respiratory movement of air have been made by H. C. Wood, Heubach, E. Orlowski, E. Vollmer, and Unverricht. The experiments of Heubach, Orlowski, Vollmer, and Unverricht were made upon animals under the influence of morphine; H. C. Wood's experiments were upon normal, morphinized, and chloralized dogs. The first effect of atropine in the normal animal is greatly to increase the respiratory air-movement. This primary excitement is usually soon followed by a decrease, which is not, however, sufficient to overcome the first rise; so that the air-movement remains for a long time distinctly above the normal. In the chloralized dog the effect of atropine in increasing air-movements is constant and pronounced. In H. C. Wood's experiments (two in number), as also in Orlowski's and Unverricht's, with animals under the influence of opium, no increase, but rather a decrease, in the air-movement was the result of injections of atropine. In Heubach's and in Vollmer's experiments, which were numerous, atropine distinctly increased the air-movement in the morphinized dog. The action of opium upon the respiration in the dog is at present so little understood that the question of the contra-action of atropine and morphine is entirely apart from that of the action of atropine. There is also reason for believing that the toxic dose of atropine paralyzes the peripheral pneumogastric nerve in the lungs, since in profound atropine-poisoning no marked influence is exerted upon the respiratory rhythm by section of the pneumogastric.

In Reichert's experiments it was found that if a dose two or three times the minimum lethal dose was given internally to the dog, the animal could be kept alive for hours by artificial respiration and ultimately recover. During the period of recovery certain remarkable phenomena habitually recurred, for an account of which the reader is referred to Reichert's article.



*Glands.*—Atropine lessens the secretion of probably all the glandular structures of the body except the kidney and possibly the intestinal glands. Its effects are especially marked upon the salivary, mammary and sweat glands. It is generally believed that the diminution in secretion is due to a paralysis of the peripheral ends of the nerves of the glands, since Keuchel has shown that stimulation of the chorda tympani fails to excite the flow of saliva, while irritation of the sympathetic will cause secretion. Mathews, however, combats this theory, and believes that the action of atropine is upon the gland-structure, asserting that nerve paralysis will not prevent secretion.

Small doses of atropine sometimes, but not always, increase the flow of urine. After the toxic dose the urine may be at first augmented, but is usually lessened very early, and may finally be entirely suppressed.\* The assertion of Meuriot, that the urinary secretion rises and falls in atropine-poisoning with the arterial pressure, is not in accord with the results obtained by Walti, who found atropine to produce in the rabbit, independently of its action upon the circulation, a steady lessening in the urinary secretion. Harley affirms that medicinal doses of atropine decidedly increase the solids of the urine, slightly the urea and uric acid, very markedly the phosphates and the sulphates.

Our knowledge of the action of atropine upon the secretions of the intestinal canal is very imperfect. It has been a matter of traditional and clinical belief that the secretions are increased, and Harley gives some experiments which he asserts corroborate this; Meuriot, on the other hand, states that they are lessened. We cannot find, however, any experiments that seem to us decisive; and clinical evidence certainly indicates that the intestinal secretions, if affected at all, are increased.

*Temperature.*—In moderate doses atropine causes a pronounced rise in temperature, but in very large decidedly toxic amounts it lessens animal heat. Thus, in the dog, Meuriot has obtained an augmentation of from 1° to 3° C., and Duméril, Demarquay, and Lecomte of 4° C. In fatal poisoning of the same animal, these observers have noticed a fall respectively of 5.10° and 3° C. In man, Meuriot, in the use of medicinal doses, has observed the temperature to rise 0.5° to 1.1° C., and Eulenburg 0.5° to 0.8° C. According to I. Ott and C. Collmar, this increase is independent of the blood-pressure, occurring both when the pressure is elevated and when it is depressed, and is accompanied by a greater increase of heat-production than of heat-dissipation. It is therefore due to the increased heat-production, which is the result, in all probability, of an influence upon the nerve-centres. Ott and Collmar believe that this influence is a stimulation of the thermo-genetic centres in the spinal cord, and that the rise of temperature is paralleled by that which occurs in tetanus. It seems to us more probable that it is due to paralysis of thermo-

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\* See case of Gross (*loc. cit.*), also of Morer (*Ann. Soc. de Méd. de Gand*, 1873).

genetic inhibition. The final fall of temperature in atropine-poisoning is probably, at least in part, caused by the vaso-motor paralysis.

*Eye.*—In all animals except birds,\* atropine causes mydriasis with paralysis of accommodation and probably lessening intra-ocular pressure. The dilatation of the pupil appears to be due to the paralysis of the peripheral terminations of the oculo-motor nerve with probably a simultaneous stimulation of the sympathetic nerve supplying the radiating fibres of the iris.

That the action of atropine upon the pupil is a local one is shown by the following facts: When instilled into one eye it causes dilatation of the pupil only on the side to which it is instilled; it is capable of dilating the pupil after section of both the trigeminus within the skull and the sympathetic within the neck; † and

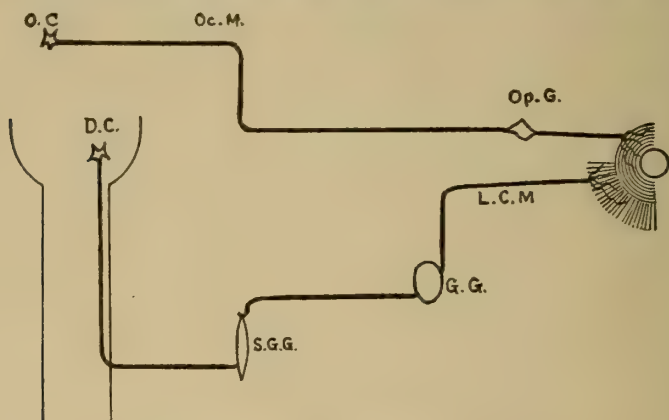


FIG. 8.—DIAGRAM OF THE INNERVATION OF THE PUPIL.

O. C.—Oculo-motor centre. Oc. M.—Oculo-motor nerve. Op. G.—Ophthalmic ganglion with nerve running to sphincter fibres of the pupils. D. C.—Dilator (sympathetic) centre in the medulla. S. G. G.—Superior cervical ganglion. G. G.—Gasserian ganglion. L. C. M.—Long ciliary nerve running to radiating fibres of pupil. Atropine paralyzes the terminals of the oculo-motor nerve in the sphincter fibres and stimulates the endings of the sympathetic nerve in the radiating fibres. Cocaine stimulates the sympathetic endings.

in the frog atropine will produce dilatation of the pupil after removal of the eye from the body (I. Hoppe, Y. Valentin). According to Borelli mydriasis is produced by the alkaloid when applied to the eye of a man just dead.

The dilatation induced by the local application of atropine is not due to a direct action of the drug upon the muscular fibres of the iris; for as all of these, both the radiating and the circular, are of the same nature (non-striated in mammals), their antagonism is simply due to position; and it seems inconceivable that mere position should affect the relations between a muscle and a drug. Moreover, Bernstein

\* The statement first made by Wharton Jones, that the reason atropine does not dilate the pupils of birds is that their irides have no radiating fibres, has been disproved by the beautiful anatomical researches of Alex. Ivanoff and Alex. Rollett (confirmed by Johannes Diegel). Although Donders says that the pupillary action of atropine "is slight in birds, in which it was formerly overlooked," in our own experiments the most thorough application of very strong solutions to the eyes of pigeons has had no distinct effect. According to the experiments of Szpilman and Luchsinger, lack of action of atropine is probably due to the muscular fibres of the irides of birds being non-striated. In the œsophagus of the bird the muscle is non-striated, and atropine paralyzes it; in the œsophagus of the rabbit the muscle is striated, and atropine has no action; in the cat a portion of the œsophagus has smooth muscular fibres, a part striated, and the former is paralyzed, the latter unaffected, by atropine.

† That this holds true for man has been shown by H. C. Wood, who, having an opportunity afforded him to give atropine hypodermically to a man whose eye had been severed from all communication with the nerve-centres, found that the pupil was still dilated by the drug.

and Dogiel (confirmed by Rossbach and Fröhlich and by G. Englehardt) found that while galvanic irritation of the oculo-motor nerve was unable to cause contraction of the pupil in the atropinized eye, yet when the electrodes were applied to the eyes in such a way as to affect directly the iris, contraction occurred,—phenomena explainable only by the theory that the nerve-endings were paralyzed, while the muscle was unaffected.

That the oculo-motor nerve is paralyzed is also shown by the fact that further dilatation of the pupil is caused by atropine after section of the cervical sympathetic. H. C. Wood has seen this effect in man after paralysis of the sympathetic. Both Donders and Stellwag von Carion insist that the paralysis of accommodation is proof of paralysis of the oculo-motor nerve, and it seems to us they do so with truth.

It is probable that the sympathetic or dilating nerve-fibres of the iris are stimulated. Claude Bernard and Lemattre both have found that atropine-mydriasis occurs in animals after section of the oculo-motor, and we have seen it in cases of complete oculo-motor paralysis in man.

Clinical experience certainly shows that the dilatation produced by a mydriatic is not merely a passive movement of relaxation, but is active, capable of tearing up inflammatory adhesions even when of some firmness. The facts that the dilatation that occurs after the destruction of the oculo-motor nerve in animals, is not at all equal to that produced by atropine, and, indeed, can be largely increased by the action of the drug, and that in the eye separated entirely from the nerve-centres (see above) atropine still causes a wide dilatation, necessitate the belief either that the alkaloid acts upon the sympathetic fibrillæ or that the peripheral fibres of a nerve are in themselves nerve-centres, acting upon the muscle of themselves even when separated from their centres. It has been urged against the view here taken that even the widest artificial mydriasis is increased by galvanization of the sympathetic. De Ruiter states the contrary; but, since Grünhagen, Hirschmann, and Englehardt separately affirm as the result of personal experiment, the correctness of the asserted fact, it must be accepted. Granting its truth, we do not think it warrants the deduction, since it is conceivable that an agent may excite the peripheral filaments of a nerve greatly, and yet not to such a point that they will be incapable of further excitation. Schultz believes there is in his experiments no stimulation of the dilator fibres, because when the superior cervical ganglion is destroyed and time allowed for the degeneration of the peripheral nerve-fibres, atropine, while dilating both pupils, does not destroy their inequality. This does not, however, seem to us to prove Schultz's conclusion, for it may well be that it is the intramuscular endings of the sympathetic nerve which are stimulated rather than the sarcolemma of the muscles themselves,—a theory rendered more probable by the fact that Schultz found that pieces of the iris of a cat, when exposed to a five-per-cent. solution of atropine, did not lose their irritability.

**SUMMARY.**—Atropine is a paralyzant to peripheral nerve terminals, affecting in this way the vagi, the motor nerves, the secretory nerves and, to a lesser extent, the sensory nerves. It is also a paralyzant to inhibition (perhaps preceded by slight stimulation), affecting the cardiac, intestinal and spinal inhibitory mechanisms. It acts upon the brain to produce delirium, in the frog it causes a state of palsy followed by motor excitation. It raises the blood-pressure by increasing the heart rate and by stimulating the vaso-motor centres; after large toxic doses there is a failure of the circulation. It is a respiratory stimulant but, after excessive quantities, may become depressant. It dilates the pupil probably by a conjoint paralysis of the oculo-motor terminals and stimulation of the sympathetic. It finally paralyzes non-striated muscles, although there is frequently a primary increase of peristalsis probably through removal of inhibition. It diminishes all secretions (except of the intestines and kidney) by an action on the nerves in the glands.



**Therapeutics.**—In practical medicine atropine is employed in direct conformity to its physiological action, so that its use is best discussed under the headings of the various indications to meet which it may be administered.

*To Relax Spasm.*—As the powers of atropine to relax spasm depend on its influence upon the peripheral nerve-filaments and the muscle-tissue, it is evident that it is a practical remedy only in those cases in which the spasm is due to some local cause connected with a muscle or its supplying nerve; hence it has been found especially useful in *rheumatic torticollis*, in the violent contractures and spasms sometimes accompanying *neuritis*, and especially such as follow *nerve-wounds*. It is essential that the alkaloid be injected directly into the contracted muscle, so as to get its concentrated influence upon the affected nerve and muscle, little or no relief usually being produced by so small an amount of the remedy as would reach the diseased part after absorption through the blood.

The non-striated muscles are more affected by the atropine than the striated, and consequently the drug is found to be more efficacious in spasm of the involuntary than of the voluntary muscles. It is serviceable in *lead colic*, in *simple spasmodic colic*, in *spasmodic dysmenorrhœa*, in *spasmodic constriction* of the bowels with *obstinate constipation*, in *laryngismus stridulus*, in *nervous cough*, in *asthma*, in *hiccough*, and in *whooping-cough*, in which last disease, as originally advised by Bretonneau, it has been largely used; also, even in the spasms accompanying the passage of *renal* and *biliary calculi*, where of course it usually fails. Wherever it is possible, it should be used locally in spasm of the involuntary as well as of the voluntary muscles. Thus, in *spasm of the urethra*, the ointment should be rubbed in along the canal; in *rigid os uteri*, the extract should be applied directly to the os; in *asthma*, belladonna should be inhaled, by means either of the cigarette or of the atomization of a decoction of the leaves; in *spasm of the sphincter ani* from *fissure* or other cause, it should be applied directly to the part by poultice or ointment. Under the present indication may be considered the use of the remedy in *constipation*. In doses of one-quarter to one-half grain (0.016–0.03 Gm.) of the extract, belladonna is of great service as an addition to laxative pills. In that form of *incontinence of urine* in children in which the real cause is an irritability of the bladder, so that spasmodic contraction occurs under the stimulus of a small portion of urine, the continuous use of large doses of atropine is often of great service by reducing the irritability of the walls of the bladder, with which, owing to the method of its excretion, the alkaloid is brought in local contact.

*To Impress the Heart and Blood-Vessels.*—In certain diseases, such as *pneumonia*, *congestion of the lungs*, etc., in which the local affection is closely connected with dilatation of the blood-vessels, Harley has highly commended atropine as a vaso-motor contractant. In most of these affections, however, the remedy has failed to establish itself.

As a stimulant to the circulation, belladonna has probably not been employed as much as it ought. Graves, however, commends it especially when the pupil is contracted in *typhus fever*, and it has been used with asserted advantage in *erysipelas*, *scarlet fever*, etc. In cases of sudden *collapse* occurring in acute disease and marked by falling of the temperature below normal, with great loss of the arterial tension and free sweating, atropine is of the greatest value. Such collapse is not infrequent in young children in the advanced stages of *pneumonia*, *pleurisy*, or other pulmonic disease, and is also prone to happen in puerperal *mania* and similar maniacal states occurring in exhausted patients. It is similar in its character to that which is produced by perforations of the stomach or intestine or as the result of surgical or accidental traumatisms. It is a condition of *shock* in which the loss of temperature is chiefly the result of vaso-motor paralysis. Proper treatment of this condition consists chiefly in the free use of external heat and the hypodermic injection of atropine, strychnine, and the tincture of digitalis; in many of these cases alcoholic stimulants are worse than useless.

*To Arrest Secretion.*—In *mercurial salivation* atropine arrests almost at once the discharge of saliva, and seemingly facilitates greatly the return to health. In *colliquative sweats*, as originally recommended by Da Costa, it is probably the most valuable known remedy. One-eightieth to one-sixtieth of a grain (0.8 to 1.0 Milligm.) of atropine used hypodermically, at bedtime, will very frequently prevent the usual *night-sweat*. In *colliquative diarrhœa* it has been recommended by M. Delpage, and very probably will be found of service. Inunctions of the breast with belladonna ointment are habitually employed for the purpose of arresting the secretion of milk, and in the experiments of Hammerbacher upon a goat, atropine given internally lessened the secretion, especially of the watery portions of milk. It is largely employed to check excessive nasal secretions as in *acute coryza* or *hay fever*.

*To Stimulate Respiration.*—It is stated that as far back as 1570 it was affirmed that opium and belladonna are, in their influence upon the system, antagonistic. But the two drugs are in no wide sense really antagonistic. Atropine, is, however, a valuable remedy in *opium-poisoning* as a respiratory stimulant. In protracted opium-narcosis the cardiac and vaso-motor actions of atropine are of service; but it should never be forgotten that the main influence for good is upon the respiratory centres. As in overdose it becomes depressant, not more than one-fiftieth of a grain should be given.

Whenever there is failure of respiration in other poisonings or diseases than that of opium, atropine in conjunction with strychnine is useful. It has been especially commended as an antidote to *poisonous fungi*.\*

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\* Atropine antagonizes the action of muscarine (the alkaloid of many of the poisonous mushrooms) on the cardiac inhibitors as well as on the respiration.

*As a Local Sedative.*—Locally and freely applied, belladonna is a sedative, and, we believe, to glandular as well as to muscular and nervous tissues. In this way it is often very useful in various local inflammations. In the form of a plaster it is frequently employed to relieve *neuralgic* and *rheumatic pains* with very doubtful benefit. The ointment is sometimes of service in painful *hemorrhoids*. In *mastitis*, its local application to the breast is often very efficacious. Whenever belladonna is used locally, in order to get its good effects it must be employed freely. At the same time, it should be remembered that a number of cases of poisoning by its external application have been reported.\* In children it must be used with caution; in adults, with a reasonable amount of care, its external use is safe, provided directions be given to have it washed off so soon as any affection of the sight or dryness of the throat is induced.

*Ophthalmic Uses.*†—The instillation of a four grains to the ounce solution of atropine sulphate into the eye is followed in about fifteen minutes by dilatation of the pupil, usually reaching its maximum in from twenty-five to thirty-five minutes, and lasting until the third day. In about twenty-five minutes the power of accommodation begins to be lost, and in from an hour and a half to two hours is usually fully annulled: return begins on the second day, but the function may not be fully regained for over a week.

Atropine is used by ophthalmologists: First, to dilate the pupil for purposes of ophthalmoscopy and to expose the lens in cases of incipient cataract so that all portions of it may be carefully examined, but is inferior in this respect to more rapidly and fugacious acting mydriatics, particularly a four-per-cent. solution of cocaine, a one-and a half-per-cent. solution of homatropine, or a ten-per-cent. solution of euphthalmine. Second, in *iritis* and *irido-cyclitis* to give rest to the iris and to prevent the development of synechia and occlusion of the pupil area with exudates; for this purpose it is the best of the mydriatics. Third, to paralyze accommodation when it is desired to determine with accuracy the refraction of the eye for the fitting of spectacles and other purposes, and to overcome spasm of accommodation; in such cases repeated instillations of the atropine solution may be necessary. Fourth, to give rest to the eye, to exert an anodyne alternative influence, and to lessen the liability to iritis in various forms of *keratitis* and *ulcers* of the cornea; in *phlyctenular keratitis* it is especially useful, and in *perforating ulcers*, particularly if they have a central situation, it overcomes the prolapse of the iris; for this purpose it must be used very freely.

The existence of *glaucoma*, or any tendency to it, is a contra-indication to the use of atropine. It may in chronic glaucoma precipitate an acute attack, and in acute glaucoma causes marked increase of pain, of congestion, and of the already excessive intra-ocular tension.

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\* See *M. T. G.*, Nov. 1856 and *London Pharm. Journ.*, 1871.

† For this section the authors are indebted to Professor George E. de Schweinitz.



**Administration.**—For nearly all purposes for which the drugs are useful atropine sulphate is preferable to the various preparations of belladonna, stramonium or scopolia, on account of the better absorption and more accurate dosage. When, however, the local action on the intestines is wished the slower absorption of the extract of belladonna makes it the preparation of choice.

In dropping an atropine solution in the eye for local effect the head should be so inclined that the fluid will run out of the outer canthus, while pressure may be applied upon the optic end of the lachrymal duct to prevent passage of the solution into the mouth. Poisoning through the local use of the remedy by ophthalmic surgeons has often occurred.

**Toxicology.**—The earliest symptoms of atropine-poisoning are a dryness of the throat and mouth with redness of the fauces, dilated pupil, disordered vision and possibly diplopia. The pulse is excessively rapid, and hard; the skin is warm and dry, and frequently an erythematous rash appears on the face and neck and sometimes spreading over the body. This eruption resembles that of scarlet fever, but lacks the punctuation and is usually not followed by desquamation. Early in the poisoning there may be forcible expulsion of urine, but later there is commonly retention. The most striking symptom in a well-developed case is the peculiar talkative wakeful delirium, sometimes associated with hallucinations or illusions. Thus, we have seen a lady remain for a long time, holding fast to the bed-post, to which she talked in the most voluble manner as though it was an intelligent living entity. Sometimes the delirium is wild and the patient almost uncontrollably violent. Respirations are at first increased in both rate and depth but after very large doses may become slow and shallow, death if it occurs being immediately due to asphyxia. In cases of fatal poisoning, stupor and muscular paralysis finally develop, sometimes preceded by convulsions.

The diagnosis, if in doubt, may be confirmed by instilling a few drops of the urine into the eye of a cat or other animal, when if the case is atropine-poisoning the pupil will be dilated. While this physiological test furnishes sufficient evidence for a working diagnosis it merely proves that the poisoning is by some mydriatic substance, not necessarily atropine. Morel calls attention to a sort of laryngitis produced by poisonous doses of belladonna, characterized by pain in the larynx, roughness of voice, and the expectoration of minute, pearly, tough pellets. It was present in the advanced stages of two cases of poisoning under his care. Raphael has noted glycosuria as a symptom of belladonna-poisoning and has experimentally produced the condition with atropine in rabbits.

The minimum fatal doses of belladonna preparations are not known.

An enema representing eighty grains of the root has produced death in five hours; \* but, on the other hand, recovery has occurred after the ingestion of three

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\* W. G. H., Feb. 1845.

drachms of the extract.\* A tenth, or even a twentieth, of a grain of atropine will often produce alarming symptoms; yet Chambers reports recovery in a child four years old who had taken about two teaspoonfuls of a solution containing a grain of the alkaloid in half an ounce, and Strachan in a child of five years from a tablespoonful of glycerin containing one-half per cent. of alkaloids.

Congestion of the lungs and of the membranes, and even of the substance of the brain and cord, may be found after death, and, according to M. Lemattre, congestion of the retina is an almost characteristic lesion.

In the *treatment* of belladonna-poisoning, the stomach should be emptied by means of emetics or the stomach-pump. The best antidote is probably the compound solution of iodine in doses of six minims, as recommended by Prescott; in the absence of this, tannic acid in twenty-grain doses may be given. The various symptoms must then be met as they arise, respiration and circulation being maintained as in other narcotic poisoning; according to Reichert, recovery may follow after a dose much larger than the maximal fatal quantity if artificial respiration be persisted in. The exact value of opium in belladonna-poisoning has not been determined, and its employment should be tentative, although good is to be expected from its judicious use. Physostigmine and pilocarpine appear to be somewhat antagonistic to atropine within certain limits, and pilocarpine has been used in atropine-poisoning. (See Physostigma and Pilocarpus.) After toxic doses of belladonna, there is generally complete retention of urine; and as this secretion contains the greater part of the ingested poison, and as reabsorption from the bladder is at least conceivable, the catheter should be used early.

### HYOSCINE.

Hyosine is defined by the Pharmacopœia as "an alkaloid chemically identical with scopolamine, obtained from hyoscyamus and other plants of the Solanaceæ." While to-day there is no longer any difference of opinion as to the chemical identity of the substance known in Germany as scopolamine with that known in this country as hyosine, there has been much difference of opinion as to the physiological identity of the two alkaloids. The experiments of the early investigators were so different in their results as to afford a certain amount of justification for the belief that the two substances were distinct in their effects. Recent investigations have, however, afforded the explanation of these differences. The alkaloid hyosine has the power of rotating polarized light to the left; certain specimens, will be much more active in their rotatory power than other specimens, although indistinguishable by any of the ordinary chemical tests. The comparative action of a specimen of hyosine which possessed a high grade of rotatory power and that which was devoid of it has been studied by Cushny and Peeble. These authors found that the

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\* Taylor's *Medical Jurisprudence*, London, 1873, 432.

effect of the two isomers upon the central nervous system was indistinguishable, but that the lævo-rotatory hyoscine was much more actively paralyzant to the inhibitory fibres of the heart and to the secretory nerves.\*

The terms hyoscine and scopolamine are applied, however, indiscriminately by manufacturers to alkaloids of all degrees of rotatory power, nor does the Pharmacopœia make any distinction. It must, therefore, be conceded that, as the terms are at present used, they are completely synonymous; that hyoscine and scopolamine are not only chemically but also physiologically and therapeutically identical.

#### Official Preparations:

Hyoscine Hydrobromidum. . . . .  $\frac{1}{300}$  to  $\frac{1}{30}$  grain (0.3 to 0.8 Milligm.).

Scopolamine Hydrobromidum. . . . .  $\frac{1}{300}$  to  $\frac{1}{30}$  grain (0.3 to 0.8 Milligm.).

**Physiological Action.**†—The effect of hyoscine upon the circulation is comparatively feeble. The differences which have been obtained by various experimenters, according to Cushny and Peebles, depend upon the variations in the degree of rotatory power of the alkaloid. With large doses of the lævo-rotatory hyoscine there is a depression of the peripheral endings of the pneumogastric nerve with consequent increase in the pulse-rate, similar to that seen after atropine; with hyoscine of low rotatory power, however, there is little or no change in the rate of the pulse, except after very large doses. In neither case does there seem to be any marked change in the blood-pressure, although Kochmann finds that small doses produce a slight rise through stimulation of the vaso-motor centre, and H. C. Wood that large doses are slightly depressant to both the heart and vascular system.

*Nervous System.*—In the higher mammals hyoscine acts as a depressant to the cerebrum. In man, if used in sufficient doses, it nearly always eventually produces sleep, although sometimes preceded by a mild degree of delirium. According to Kochmann the electrical irritation of the psycho-motor area is lessened by the drug, and there is no analgesia during the sleep.

In the frog hyoscine causes a lessening of the reflex action, which H. C. Wood attributed to the depression of the motor side of the spinal cord but which Cushny and Peebles believe is a result of the depressant action upon the peripheral endings of the motor nerves. Parisot asserts that after large doses a stage of excitement follows the depression similar to that caused by atropine.

*Respiration.*—According to both Wood and Kochmann hyoscine acts as a depressant to the respiration, although it requires comparatively large doses to produce any marked alteration in this function. In fatal poisoning by the drug death is always due to asphyxia. In

\* Kessel (*A. I. P.*, xvi, 1) was, however, unable to detect any difference in the effects of three samples of scopolamine ranging in their rotatory power from 0 to  $-14.7^\circ$ .

† It has not been thought necessary to discuss in detail the older investigations concerning the physiological effects of hyoscine as the differences between the polarizable and non-polarizable alkaloid was not then recognized. The most important papers are those of Wood, of Kochmann, of Claussens, and of Kobert.



this connection it is interesting to note that in the dog, as in man, it is almost impossible to kill with a single dose of hyoscyne; Kochmann has injected as much as seven and one-half grains (0.5 Gm.) into a small dog intravenously without destroying life.

*Secretions.*—Upon the secretions hyoscyne acts much like atropine, producing lessening in the saliva, and, according to Kochmann, also in the sweat and mucous secretions. In cases of human poisoning, however, the skin is usually covered with moisture.

*Pupil.*—Upon the pupil hyoscyne acts like atropine, a half of one-per-cent. solution rapidly paralyzing accommodation and dilating the pupil. It is said that it does not produce any irritation, and that its maximum effects are reached in one-third the time necessary for those of atropine, and are more permanent and less affected by eserine.\* Gley and Rondeau have found that the mydriasis is not prevented by previous destruction of the cervical sympathetic in the rabbit, and that irritation of the sympathetic nerve will increase the dilatation.

**SUMMARY.**—The dominant physiological action of hyoscyne is upon the cerebral cortex, producing sleep often accompanied by a low delirium. It is also a centric depressant of respiration, and depresses, though somewhat feebly, the whole motor cord: upon the sexual centres it acts more powerfully. Its influence upon the circulation is very slight. On the mucous membrane and probably on the muscles of the throat it acts powerfully, suppressing secretion and interfering with function.

**Therapeutics.**—Hyoscyne is a valuable hypnotic in those forms of insomnia in which sleep is banished by a continual flow of thoughts or mental images passing through an excited brain; hence it is often very effective in the insomnia of *delirium*, of *acute mania*, or of other forms of *insanity*. In some cases of insanity with cerebral excitement most excellent results are produced by the administration every three to five hours of small doses that will calm without causing sleep. As an hypnotic the alkaloid lends itself very well to combinations, intensifying greatly the influence of morphine, chloral, trional, and other drugs of the class. In cases of severe kidney disease it would seem to be a safer hypnotic than is morphine, and as it has no sedative influence upon the heart, it may be used when the feeble condition of that viscus forbids chloral.

The use of enormous doses (one-fiftieth to one-twentieth of a grain) of hyoscyne as a curative remedy in *acute insanity* has been advocated by H. R. Costons, and a remarkable case is recorded by Balagopal, in which one-sixth of a grain was given hypodermically to a patient suffering from violent, *acute mania*. Immediately after the injection the patient fell, crying that he was dying; his face became deadly pale, the conjunctiva insensitive, the breathing difficult and stertorous, the limbs spasmodically contracted. After

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\* John Tweedy, *Lancet*, Dec. 1886.

recovery, which occurred without remedies other than hypodermic injections of ether, the patient's mental condition rapidly improved, and in a week he was well.

Probably through its influence upon the spinal centres hyoscine is useful in all cases of *sexual excitement*, such as *nymphomania*, *spermatorrhæa*, and allied affections. It is the most certain remedy that we have in ordinary cases of over-frequent *seminal emissions*, which can usually be controlled by the administration of the one-hundred-and-twentieth to one-eightieth of a grain on going to bed.

As an analgesic hyoscine is of little value, though Winnett states that it is very serviceable in the crises of *locomotor ataxia*. It has been used to a considerable extent in certain spasmodic disorders. Edlesen, as early as 1881, affirmed its value in *asthma* and *whooping-cough*. Erb has used it with advantage in various spasms. In *spinal accessory spasm* it has, in our hands, failed. On the other hand, in pronounced *paralysis agitans*, attended by much aching pain, we have seen it give very great relief from both pain and tremors. Usually in these cases it should be administered only at bedtime, as it is merely a palliative, and if used continually is prone to lose its power.

In 1900 Schneiderlin suggested the hypodermic injections of large doses of morphine and scopolamine for the production of surgical anesthesia. In this method doses ranging from one-sixth to one-half grain of morphine in conjunction with from one-hundredth to one-fiftieth grain of hyoscine are injected an hour before the operation. The idea was founded on an erroneous conception of the physiological action of hyoscine, which is in no proper sense the antagonist of morphine and possesses but feeble analgesic properties. H. C. Wood, Jr., collected the reports of nearly 2000 cases, with 9 deaths, giving the frightful mortality of 1:221. Moreover in 69 per cent. of the cases ether or chloroform was required to produce sufficient anesthesia for operation. It is possible that in certain classes of cases the method may occasionally prove of value, but as a routine measure it cannot be too strongly condemned.

**Administration.**—The action of hyoscine given hypodermically is manifested inside of ten minutes, and lasts from six to eight hours. In severe excitement, especially that of violent insanity, the dose should be repeated every six or eight hours. The dose for hypodermic use is from the one-hundred-and-fiftieth to one-eightieth of a grain (0.6–0.8 milligramme). Excessive susceptibility to the action of hyoscine being a not infrequent idiosyncrasy, it is best to give at first amounts below the minimum dose here stated. The tastelessness of hyoscine makes it easy to administer to insane or other patients without their knowledge.

Owing to its great influence upon the throat, hyoscine is strongly contraindicated in cases of acute disease of the throat. Thus, we have seen it, when given in violent *anginose scarlatina* with delirium, cause such rapid increase in the difficulty of respiration as to suggest that it played an important rôle in the production of the fatal asphyxia.

**Toxicology.**—The symptoms which are produced in man by decided doses of hyoscine are dryness of the mouth, flushing of the face, great sleepiness, associated in some cases with semi-delirious mutterings, and a feeling of giddiness like that of intoxication. The respirations are lessened in frequency and mydriasis is usually, but not always pronounced. After very large doses the symptoms mentioned are more intense, the pupils dilated, the mouth and throat excessively dry, and the voice hoarse or even partially suppressed, probably from paralysis of the vocal cords.

The pulse-rate is usually not much altered, very frequently being slower than normal but in other instances has been rapid. The respirations are slow and full, and are said by H. M. Wetherill to be sometimes Cheyne-Stokes. The face and the general surface of the body are suffused, muscular relaxation is pronounced, and loss of coördination usually very evident. The skin, so far from being abnormally dry, is commonly bathed in perspiration. Several observers assert also that there is a rise of temperature. Sometimes the delirium is active, accompanied by visual hallucinations, and clonic convulsions with opisthotonos have been noted. Mairé and Combeval found that monkeys when poisoned by it gave evidences of the presence of hallucinations, such as are sometimes produced in man. No fatal case of poisoning by hyoscine is on record.

H. A. Hutchinson took a quarter of a grain of an impure hyoscine: quiet coma with entire muscular relaxation was produced, and lasted eleven hours. The fiftieth of a grain has, however, several times caused very alarming symptoms, and much smaller doses are affirmed to have produced serious effects (see Carey).

O'Hara saw one-ninety-sixth of a grain administered hypodermically produce very severe disturbance, lasting for twenty-eight hours, with total lack of remembrance of occurrences which took place during the seven hours following the injection; while Root asserts that one-three-hundredth of a grain given by the mouth produced violent poisoning, and even one-twelve-hundredth very pronounced symptoms. The dispensing of such minute quantities of a drug is so difficult that it is probable that more of the alkaloid was given than is alleged.

**HOMATROPINE HYDROBROMIDE.** *Homatropinæ Hydrobromidum.*—Homatropine is an alkaloid artificially produced from tropine, the *hydrobromide* of which is preferred for practical use on account of its being stable and not hygroscopic. It is said to cause, when taken internally, symptoms similar to those caused by atropine,\* except in regard to the circulation. The retardation of the pulse has been proved by Tweedy and Ringer, Beyer, and De Schweinitz and Hare to be, at least in part, the result of a direct action of the drug upon the heart-muscle or its contained ganglia, since in the frog and in the terrapin the application of homatropine hydrobromide to the exposed heart *in situ* reduces very greatly the number of the beats. In the dog injection of the alkaloid into the jugular vein is followed by a fall of as much as thirty or forty beats per minute, which De

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\* Brown (*Ann. of Ophthalm.*, xv, 237) reports delirium following instillation of two drops of a two-per-cent. homatropine solution in each eye.



Schweinitz and Hare believe to be in part due to stimulation of the vagi nerves, because section of the vagi causes a marked increase in the pulse-rate, "although not such a rise as would appear if the inhibitory apparatus was intact." De Schweinitz and Hare found that the fall of the pulse-rate was accompanied by a marked fall of the arterial pressure. Since the production of asphyxia was followed at this time by a pronounced rise in the arterial pressure, it would appear that the fall of pressure is not the result of a vaso-motor paralysis, but of the cardiac influence of the drug.

It has been shown by the experiments of Tweedy and Ringer, confirmed by De Schweinitz and Hare, that homatropine produces in the frog a brief period of tetanus, followed by absolute muscular relaxation, with abolition of reflex and voluntary activity, followed in from six to eight hours, if the dose has been properly proportioned, by return of voluntary movements, associated with tetanic spasms of great intensity. The convulsive movements and the paralysis are, according to De Schweinitz and Hare, of spinal origin, as the nerve-trunks and muscles are not affected. The cause of death is centric respiratory paralysis.

The influence of the alkaloid upon the eye is practically identical with that of atropine, except that it is somewhat more feeble and is much more temporary. The pupil begins to dilate in from seven to twenty minutes after the instillation of the drug, and accommodation fails in from forty to ninety minutes; in from one to seventy-two hours the recovery is complete. According to De Schweinitz, a solution of one in eighty is sufficiently strong to paralyze accommodation completely, provided it be dropped repeatedly into the eye. When it is desired simply to dilate the pupil for ophthalmoscopic examinations, a single application of a solution of four grains to the ounce suffices. Homatropine as a practical mydriatic has the advantage of fugaciousness of action, of being not at all irritant, and of being little prone to produce systemic disturbance.

### INDIAN CANNABIS.

*Cannabis Indica* is the dried flowering tops of the female plants of *Cannabis sativa*, or hemp, grown in India. According to most modern botanists, the Indian plant is the same species as the familiar hemp plant cultivated in this country, as well as parts of Europe. H. C. Wood has shown that the American plant possesses the same physiological properties as that grown in India. In the East hemp and its educts are used as narcotic stimulants. *Gunjah* is the dried plant as sold in the bazaars of Calcutta for smoking. *Churrhus*, known in Egypt as *hashish*, is the resinous exudation with the epidermis, etc., scraped off the leaves.

Indian Cannabis occurs in commerce in greenish brown compressed masses markedly coherent from the large amount of resinous exudate. It has a peculiar narcotic odor and bitterish and somewhat acrid taste.

Various substances have been announced as the active principle of *cannabis indica*,—*cannabin*, *cannabinon*, *tetano-cannabene*, *orycannabin*, *cannabene*, etc. *Cannabinol* of Wood, Spivey, and Easterfield is, according to Fraenkel, inert, and should be known as *pseudocannabinol*, the name *cannabinol* being retained for a distinct substance which he, Fraenkel, has isolated and found to be active.

#### Official Preparations :

Extractum Cannabis Indicæ.....	$\frac{1}{8}$ to $\frac{1}{4}$ grain (0.01–0.016 Gm.).
Fluidextractum Cannabis Indicæ.....	1 minim (0.06 C.c.).
Tinctura Cannabis Indicæ (10 per cent.) ...	10 to 20 minims (0.6–1.2 C.c.).

**Physiological Action.**—When given in full doses, *cannabis indica* produces a feeling of exhilaration, with a condition of revery, and a train of mental and nervous phenomena which varies very much according to the temperament or idiosyncrasies of the subject, and very probably also, to some extent, according to the nature of his surroundings. The sensations are generally spoken of as very pleasurable; often beautiful visions float before the eyes, and a sense of ecstasy fills the whole being; sometimes the venereal appetites are greatly excited; sometimes loud laughter, constant giggling, and other indications of mirth are present. Some years since, in experimenting with an extract made from the American plant, H. C. Wood took a large dose, and described the results as follows:

“About half-past four P.M., September 23, I took most of the extract. No immediate symptoms were produced. About seven P.M. a professional call was requested, and, forgetting all about the hemp, I went out and saw my patient. While writing the prescription, I became perfectly oblivious to surrounding objects, but went on writing, without any check to or deviation from the ordinary series of mental acts connected with the process, at least that I am aware of. When the recipe was finished, I suddenly recollected where I was, and, looking up, saw my patient sitting quietly before me. The conviction was irresistible that I had sat thus many minutes, perhaps hours, and directly the idea fastened itself that the hemp had commenced to act, and had thrown me into a trance-like state of considerable duration, during which I had been stupidly sitting before my wondering patient. I hastily arose and apologized for remaining so long, but was assured I had only been a very few minutes. About seven and a half P.M. I returned home. I was by this time quite excited, and the feeling of hilarity now rapidly increased. It was not a sensuous feeling, in the ordinary meaning of the term; it was not merely an intellectual excitation; it was a sort of *bien-être*,—the very opposite to *malaise*. It did not come from without; it was not connected with any passion or sense. It was simply a feeling of inner joyousness; the heart seemed buoyant beyond all trouble; the whole system felt as though all sense of fatigue were forever banished; the mind gladly ran riot, free constantly to leap from one idea to another, apparently unbound from its ordinary laws. I was disposed to laugh; to make comic gestures; one very frequently recurrent fancy was to imitate with the arms the motions of a fiddler, and with the lips the tune he was supposed to be playing. There was nothing like wild delirium, nor any hallucinations that I remember. At no time had I any visions, or at least any that I can now call to mind; but a person who was with me at that time states that once I raised my head and exclaimed, ‘Oh, the mountains! the mountains!’ While I was performing the various antics already alluded to, I knew very well I was acting exceedingly foolishly, but could not control myself. I think it was about eight o’clock when I began to have a feeling of numbness in my limbs, also a sense of general uneasiness and un-

rest, and a fear lest I had taken an overdose. I now constantly walked about the house; my skin to myself was warm, in fact my whole surface felt flushed; my mouth and throat were very dry; my legs put on a strange, foreign feeling, as though they were not a part of my body. I counted my pulse and found it one hundred and twenty, quite full and strong. A foreboding, an undefined, horrible fear, as of impending death, now commenced to creep over me; in haste I sent for medical aid. The curious sensations in my limbs increased. My legs felt as though they were waxen pillars beneath me. I remember feeling them with my hand and finding them, as I thought at least, very firm, the muscles all in a state of tonic contraction. About eight o'clock I began to have marked 'spells,'—periods when all connection seemed to be severed between the external world and myself. I might be said to have been unconscious during these times, in so far that I was oblivious to all external objects, but on coming out of one it was not a blank, dreamless void upon which I looked back, a mere empty space, but rather a period of active but aimless life. I do not think there was any connected thought in them; they appeared to be simply wild reveries, without any binding cord,—each a mere chaos of disjointed ideas. The mind seemed freed from all its ordinary laws of association, so that it passed from idea to idea, as it were, perfectly at random. The duration of these spells to me was very great, although they really lasted but from a few seconds to a minute or two. Indeed, I now entirely lost my power of measuring time. Seconds were hours; minutes were days; hours were infinite. Still, I was perfectly conscious during the intermissions between the paroxysms. I would look at my watch, and then after an hour or two, as I thought, would look again and find that scarcely five minutes had elapsed. I would gaze at its face in deep disgust, the minute-hand seemingly motionless, as though graven in the face itself; the laggard second-hand moving slowly, so slowly. It appeared a hopeless task to watch during its whole infinite round of a minute, and always would I give up in despair before the sixty seconds had elapsed. Occasionally, when my mind was most lucid, there was in it a sort of duplex action in regard to the duration of time. I would think to myself, it has been so long since a certain event,—an hour, for example, since the doctor came; and then reason would say, No, it has been only a few minutes; your thoughts or feelings are caused by the hemp. Nevertheless, I was not able to shake off this sense of the almost indefinite prolongation of time, even for a minute. The paroxysms already alluded to were not accompanied by muscular relaxation. About a quarter before nine o'clock, I was standing at the door, anxiously watching for the doctor, and when the spells would come on I would remain standing, leaning slightly, perhaps, against the door-way. After a while I saw a man approaching, whom I took to be the doctor. The sounds of his steps told me he was walking very rapidly, and he was under a gas-lamp, not more than one-fourth of a square distant, yet he appeared a vast distance away, and a corresponding time approaching. This was the only occasion on which I noticed an exaggeration of distance; in the room it was not perceptible. My extremities now began to grow cold, and I went into the house. I do not remember further, until I was aroused by the doctor shaking or calling me. Then intellection seemed pretty good. I narrated what I had done and suffered, and told the doctor my opinion was that an emetic was indicated, both to remove any of the extract still remaining in my stomach, and also to arouse the nervous system. I further suggested our going into the office, as more suitable than the parlor, where we then were. There was at this time a very marked sense of numbness in my limbs, and what the doctor said was a hard pinch produced no pain. When I attempted to walk up-stairs, my legs seemed as though their lower halves were made of lead. After this there were no new symptoms, only an intensifying of those already mentioned. The periods of unconsciousness became at once longer and more frequent, and during their absence intellection was more imperfect, although when thoroughly roused I thought I reasoned and judged clearly. The oppressive feeling of impending death became more intense. It was horrible. Each paroxysm would seem to have been the longest I had suffered; as I came out of it, a voice seemed constantly saying, 'You are getting worse; your paroxysms are growing longer and deeper; they will overmaster you; you will



die.' A sense of personal antagonism between my will-power and myself, as affected by the drug, grew very strong. I felt as though my only chance was to struggle against these paroxysms,—that I must constantly arouse myself by an effort of will; and that effort was made with infinite toil and pain. I felt as if some evil spirit had control of the whole of me except the will-power, and was in determined conflict with that, the last citadel of my being. I have never experienced anything like the fearful sense of almost hopeless anguish and utter weariness which was upon me. Once or twice during a paroxysm I had what might be called nightmare sensations: I felt myself mounting upward, expanding, dilating, dissolving into the wide confines of space, overwhelmed by a horrible, rending, unutterable despair. Then, with tremendous effort, I seemed to shake this off, and to start up with the shuddering thought, Next time you will not be able to throw this off, and what then? Under the influence of an emetic I vomited freely, without nausea, and without much relief. About midnight, at the suggestion of the doctors, I went up-stairs to bed. My legs and feet seemed so heavy I could scarcely move them, and it was as much as I could do to walk with help. I have no recollection whatever of being undressed, but am told I went immediately to sleep. When I awoke, early in the morning, my mind was at first clear, but in a few minutes the paroxysms, similar to those of the evening, came on again, and recurred at more or less brief intervals until late in the afternoon. All of the day there was marked anesthesia of the skin. At no time were there any aphrodisiac feelings produced. There was a pronounced increase of the urinary secretion. There were no after-effects, such as nausea, headache, or constipation of the bowels."

The sense of prolongation of time present in most cases of hemp intoxication is evidently due to the immense rapidity of the succession of ideas. The mind measures time by the duration of its own processes, and when an infinitude of ideas arise before it in the time usually occupied by a few, time becomes infinitely prolonged to the mind. It is a lifetime in the minute. A very common mental phenomenon, not easily explained unless as a result of disassociation of the cerebral hemispheres, is a condition of double consciousness, a sense of having two existences, of being at the same time one's self and somebody else.

In some cases Indian hemp produces, in addition to or even in the place of the symptom already spoken of, marked disturbances of motility. Convulsions have been noticed by Lawrie, and local spasms, with salaam convulsions, by F. H. Brown. According to O'Shaughnessy, the induction of catalepsy is not rare among the Hindoos.

Whatever may be the symptoms of the first stage, sooner or later, if the dose be sufficient, drowsiness comes on. Generally, before it is marked, partial anesthesia, often with partial loss of strength, is manifested, especially in the lower limbs. The pupils are dilated, the pulse is quickened, and finally the subject falls into a heavy sleep, out of which he generally awakes hungry, without any of the wretched gastric sensations or the malaise felt after an opiate. Confusion of thought, however, may persist for some hours. Cannabis exerts no constipating influence upon the bowels, and appears to increase, rather than decrease, the excretion of the kidneys.

In the dog, hemp extract causes exaltation followed by profound sleep (Hans Zeitler, H. A. Hare). That the drug has very little influence upon the vital functions is shown by the enormous amounts required to kill. Hare noted both in the dog and in the frog heightened,

followed by markedly lessened, reflex activity. The loss of reflex activity was the result of an influence exerted upon the sensory side of the cord or upon the sensory nerve-trunk, the anesthesia in the frog being complete at a time when voluntary movement was preserved; further, when the drug was applied directly to the nerve-trunk it produced sensory palsy. Although probably a local anesthetic, *cannabis indica* is too irritant to be applied to delicate mucous membranes.

**Therapeutics.**—Hemp has been used in this country chiefly for the *relief of pain*, but also to some extent as an *hypnotic*. As an *analgesic*, it is very much inferior to opium, but may be tried when the latter is for any reason contraindicated. In full doses, in *neuralgic* pains, it certainly often gives relief. It has been very largely employed to induce euthanasia in the advanced stages of *phthisis*, and constitutes, it is said, a popular nostrum employed for that purpose. In *tetanus*, Indian hemp has been used quite largely, and is sometimes apparently an aid to other remedies; it should be given to intoxication. As first suggested by Seguin, hemp extract, administered for months continuously in such doses as will keep just within the limit of distinct physiological effects, is often effective in *migraine*.

**Administration.**—Extract of hemp is a very unsatisfactory drug from the fact that one-eighth of a grain of one extract will produce decided intoxication, and many grains can be taken of another extract that cannot be distinguished physically or chemically from the first specimen. The only way of using it with advantage is for the practitioner to try various samples in ascending doses, and use those which are active in the dose which he has found to be effective. The foreign extracts are, on the whole, more reliable than those made in America. It should always be borne in mind that, though the symptoms may seem alarming, there is much less danger in intoxication from hemp than from alcohol. No cases of fatal poisoning have been recorded. Notwithstanding the assertions of Fronmüller and Hiller, the *tannate of cannabene* of Merck has in our trials of it seemed to be inert.

### COCA.

Two varieties of Coca leaves are recognized by the U. S. Pharmacopœia, those derived from the *Erythroxylon coca* (known as Huanuco or Bolivian Coca) and those from the *E. truxillense* (Truxillo or Peruvian Coca). Both of these shrubs are natives of South America and are cultivated to a large extent, especially on the slopes of the Andes. The annual output is estimated at eighty million pounds, most of which is consumed in South America.

Coca leaves are one to two inches in length, elliptical or oval in shape, not dentate and are distinguished from other medicinal leaves by a slightly curved line, running from the base to the apex, on each side of the midrib, and produced by the peculiar folding of the leaf in the bud.

Their odor, especially of the Truxillo variety, resembles that of tea leaves, the taste is bitterish and leaves a peculiar numbness in the mouth and lips. Coca depends for its activity on the presence of *cocaine*, of which alkaloid it contains about one-half of one per cent. Cocaine occurs in colorless, transparent prisms, soluble in six hundred parts of water, and forms with the acids very bitter, soluble, crystallizable salts. By prolonged boiling it is decomposed into methyl alcohol, benzoic acid and a substance known as ecgonine. Besides cocaine, the leaves contain a peculiar tannin, known as *coca-tannic acid*.

#### Official Preparations :

Fluidextractum Cocæ.....	$\frac{1}{2}$ to 2 fluidrachms (2-8 C.c.).
Vinum Cocæ (6½ per cent.).....	$\frac{1}{2}$ to 1 fluidounce (15-30 C.c.).
Cocaina.....	$\frac{1}{4}$ to $\frac{1}{2}$ grain (0.016-0.03 Gm.).
Cocainæ Hydrochloridum.....	$\frac{1}{4}$ to $\frac{1}{2}$ grain (0.016-0.03 Gm.).
Oleatum Cocainæ (5 per cent.).....	External use.

*Local Action.*—Locally applied, cocaine acts as a very distinct and certain anesthetic, as was noted by Moreno y Maiz in 1862, and by Von Anrep in 1880, although it was not until September, 1884, that Karl Koller demonstrated the practical value of the drug. According to the observations of Von Anrep, the nerves of special sense are as readily affected as are those of common sensibility: thus, cocaine placed upon the tongue abolishes at the place of contact, for the time being, the sense of taste. At the point of contact there is at first marked pallor, but after a short time very pronounced redness. In sensitive membranes like the conjunctiva, cocaine also causes at first much pain. The primary pallor is alleged to be due to a very powerful constriction of the small blood-vessels, and has led F. H. Bosworth to the conclusion that cocaine produces *rigid contraction in unstripped muscular fibres* whenever it comes in contact with them. The anesthesia is not, however, due to any spasm of the vessels, but to a direct action upon the nerve-trunk. Applied to the bared nerve, cocaine paralyzes first the sensitive and afterwards the motor fibres (Feinberg). Arloing asserts that the concentrated solution of cocaine placed on the bared nerve produces a distinct organic change in the nerve.

According to the experiments of Peter Albertoni and of B. Danilewsky, cocaine in sufficient concentration acts upon all forms of protoplasm, first exciting and then paralyzing functional activity.

*Absorption and Elimination.*—The soluble salts of cocaine are absorbed with great rapidity. They have the power of passing with almost equal ease through all mucous membranes, so that their absorption is almost immediate when they are employed locally in the nose, urethra, or other part; hence the large number of serious poisonings which have resulted from their local use. The ultimate fate of cocaine in the body is at present somewhat uncertain. It appears to escape to some extent through the urine unchanged (Thomas Moreno y Maiz and others), but the amount that has been recovered by chemists has been so small (five per cent., Wiechowski) as to lead to the wide-



spread belief that the alkaloid is in great part destroyed in the system; Glasenap believes that he has found *ecgonine*, a decomposition product, in the urine.

**Physiological Action.**—From the days of the Incas the leaves of the coca plant have been enormously used by the natives of Western South America as a stimulant. Mixed with ashes or a little lime, they are chewed, and are said to increase greatly for the time being the muscular strength and endurance. Moderate doses appear to increase temporarily, to a very extraordinary degree, both physical and mental power. Various travellers concur in praising the peculiar sense of calm and happiness, the insensibility to fatigue, and the increase of bodily and mental activity which the drug produces.

Montegazza states that when he took two hundred grains of the leaves he was in a short time plunged into a condition of peculiar delirious beatitude, in which he seemed to be isolated from the rest of the world and to live in a peculiar atmosphere of active calm. In a little while there came also a sense of plenitude of power which was accompanied by a real increase of physical ability, so that gymnastics which in his ordinary condition were impossible to him became easy. This state was succeeded by a natural profound sleep, lasting sometimes for twenty-four hours.

Thus, on one occasion Montegazza took thirty-five grammes, and an hour later nine grammes, etc., until he had taken in the course of two hours sixty grammes in all. The heart, which after the earliest dose had been slow in its action, directly after the second dose suddenly became rapid and very violent in its beats; but at the end of the two hours the palpitations had ceased, although the pulse was still 128 per minute. There was now a condition of intoxication similar to that which is produced by hashish. Montegazza was possessed by a feeling of intense beatitude and inner joyousness, while a succession of visions and phantasmagoria, most brilliant in color and form, trooped rapidly before his eyes. He rapidly passed into a delirious condition, in which he appeared to himself to be unconscious, although when addressed he would answer rationally. An hour or two later he was sufficiently calm to say to his friends "that God was unjust, in that He had made man to live without eating coca. I prefer a life of ten years of coca to one of a thousand years without it." As this state was passing off, he was seized with an almost irresistible desire to reproduce its delirium by taking more coca. Finally, however, he fell into a condition of sleep, which lasted only three hours. After this he was able to resume at once his ordinary occupations, and offered no physical evidence of his coca debauch.

Pronounced aphrodisiac properties have been attributed to coca, but they seem to rest upon tradition rather than upon demonstrated experience. According to M. Unanne, the ancient inhabitants of Peru represented Venus by a female figure with a coca-leaf in her hand, and the coca still plays an important part in the nuptial ceremonies of the Indians.

It has been affirmed by Tschudy and Unanne that coca is able to take the place of food; but this is clearly not the case. Weddell himself states that although an Indian chewing the coca could go on foot many hours without fatigue and without food, yet at the end he would eat more at one repast than he himself would take in two days. He accords with Bibra in stating that coca has the power of putting aside for some time the sense of hunger. While, however, it may mask the appetite, it certainly does not nourish the body, and it is

indeed most probable that the absence of hunger is the outcome of a local benumbing of the gastric nerves. Thomas Moreno y Maiz made several crucial experiments by keeping animals in pairs without food, and giving to one coca freely. These experiments have been repeated by B. von Anrep, and in every case the animal which received the coca died at least as early as its mate.

Very small doses (one- to three-one-hundredths of a grain of cocaine) produce in the frog no other symptoms than some evidences of excitement. After doses of from one-tenth to one-fiftieth of a grain the frog becomes quiet, with an apparent increase, however, in the reflex activity, sometimes amounting to tetanus, followed by increasing palsy and failure of the respiration; very large doses produce symptoms of paralysis.

In the domestic animals the symptoms vary. In the rabbit there is first a peculiar state of quiet, followed in a few moments by a condition of great excitement, in which the animal springs and jumps about. A few minutes later the rabbit again becomes quiet, and now, although trembling much, is so weak that he moves with difficulty. The tremblings increase until they merge in convulsive movements of the legs, while at the same time there is partial paraplegia; pendulum movements of the head are very marked, and finally epileptiform convulsions appear, while simultaneously a peculiar tetanic rigidity seems to indicate spinal excitement. The lethal dose for a rabbit is put at a grain and a half per kilo. Dogs and cats are said to be more susceptible to the action of cocaine than is the rabbit, and to suffer similar symptoms, but especially with the dog the evidences of mental excitement are more pronounced.

According to Von Anrep, after an injection of cocaine the dog will dance and leap, never standing still for a moment, and continually circling around the experimenter. The movements are not at all those of convulsions, but voluntary, and accompanied by every expression of joy and exhilaration. This may continue for hours, the animal then becoming gradually quiet, and passing finally into his normal condition. If instead of a moderate dose a toxic one has been given, there is first a period in which the animal is very restless but seems full of terror and anxiety; the least sound frightens him, causing him to tremble and to drop his tail between his legs. He does not appear at this time to know his master. Rhythmical movements of almost all portions of the body accompany this state. Fifteen or twenty minutes later the mental condition alters, and the dog becomes apparently full of joyous excitement. He barks loudly, runs from one person to another, licking them, and giving all the characteristic signs of joy. After a few moments this condition gives way to one of increasing feebleness; the dog gradually becomes unable to move, rhythmical movements, cramps, and convulsive symptoms appear; the pendulum-like swinging of the head gets very violent, and at last narcosis, with epileptiform convulsions, develops. It is evident that many of these symptoms are psychical.

*Nervous System.*—Moderate doses of cocaine apparently act as a stimulant to the whole central nervous system. The effect upon the brain is shown by the increase of intellectual activity as well as by the stimulation of the psycho-motor area. The reflexes are exaggerated through the stimulant influence of the drug upon the spinal cord. After large doses convulsions may occur which may be in part of cerebral origin but are certainly also due at least in part to the excitation of the cord. X After toxic doses there occurs a secondary depression of the spinal cord. In the frog cocaine is capable of causing a paralysis of both sensory and motor nerves, but in the mammal such effect can be brought out only by the local application, on account

of the powerful influence of the drug upon the respiration. Its action upon the sensory nerves is distinctly more powerful than its effect upon the motor nerves.

L. Dadd states that distinct histological changes can be recognized in the cells of the nerve-centres as the result of poisoning with cocaine, and that these lesions are most marked in the cerebral cortex.

B. von Anrep believes that the drug has a very distinct and peculiar influence upon the *semicircular canals*, thereby causing the peculiar pendulum-like motions of the head, the lack of coördination, and the rolling convulsions especially seen in doves.

According to the researches of Von Anrep, the convulsive movements are of cerebral origin, and are arrested by section of the spinal cord; but the experiments of L. I. Tumass indicate that they do not arise in the psycho-motor centres of the brain-cortex, since he found not only that the local application of cocaine lessens the irritability of these centres, but also that during the convulsive stage of cocaine-poisoning the centres are less sensitive than normal. Danini, moreover, appears to have found that section of the cord does not prevent convulsions in the hind feet, and the experiments of Mosso show that when the upper cord is cut in the dog and the animal cocaineized, the irritation of the nerve-trunk or of the surface will produce in a little while general muscular rigidity. Both Mosso and Von Anrep are in accord with other observers in stating that reflex activity is at first increased by cocaine. The motor paralysis and the loss of reflex activity which finally occur in cocaine-poisoning are probably in part the result of an influence upon the nerves; but that they are chiefly due to a direct sedative action upon the spinal cord seems to follow from the experiments of Mosso, who found that when he so bound the hind legs of the frog as to prevent the access of cocaine to the nerves, there was a rapid loss of reflex activity, and indeed a complete paralysis, at a time when both the motor and the sensory nerves were still intact.

An observation made at a certain stage of the poisoning by Dr. Ott—viz., that irritation of the posterior column of the spinal cord produced no effect, while a prick of the anterior column was followed by the usual result—indicates that there is the same difference in action upon the sensory and motor tracts as upon the corresponding nerve-trunks; but Mosso's experiments upon tritons led him to conclude that the power of conducting impulses efferently, or *from* the centre, is first lost in the spinal cord poisoned with cocaine.

Almost all observers agree that the *sensory nerves* after sufficient doses are finally paralyzed in cocaine-poisoning; but Mosso believes that the respiratory centre is more susceptible to the action of cocaine than are the sensory nerves, and certainly doses of the alkaloid not dangerous to life have no perceptible general effect upon the sensory nerves of mammals. The experiments of Nikolsky, of B. von Anrep, of Ott, and of Laffont seem to prove that the sensory paralysis is preceded by increased functional activity, which is in accord with the observation of Mosso, that in doses of 0.05 to 0.1 gramme cocaine increases in man the sensibility of the skin.

According to Danini, the *motor nerves* in the frog remain irritable until after death; but, according to Nikolsky, their functional activity is first increased and afterwards destroyed. Ott, Mosso, and Popielski agree that cocaine depresses the motor nerves. Moreno y Maiz found that when he tied the iliac artery of a frog on one side and administered cocaine anteriorly, there came a time when irritation of the poisoned limb caused no movement, while irritation of the protected extremity provoked very distinct general reflexes; at the same time there was diminished motility in the non-protected limb as compared with the protected one: facts which, of course, indicate that the drug finally depresses both motor and sensory fibres, but that its action upon the motor is subordinate to that upon the sensory nerves. H. Alms found that a five-per-cent. solution of cocaine in contact with the isolated ischiatic plexus of the frog caused absolute anesthesia of the leg and apparent loss of motor power, the leg lying motionless and trailing behind. Nevertheless, strong irritation upon the front leg of the frog caused immediate move-



ments which were shared by the cocainized hind leg, showing that the motor filaments were not paralyzed. The experiments of Alms indicate that the extreme peripheral filaments of the nerve are first affected, since at a certain period most severe irritation of the skin produced no pain in the poisoned rabbit, although the injection of irritating materials evidently caused violent pain.

According to Verebély and Horváth, the action of cocaine upon the nerve-endings is so pronounced that demonstrable changes can be noted after it has been applied locally.

*Circulation.*—The action of cocaine upon the circulation is in some details so complex that in spite of much work it is not yet fully understood, but in the main our knowledge concerning it is clear. It produces a rise in pressure which is chiefly due to the stimulation of the vaso-motor centre in the medulla, although there is some evidence that the heart is also stimulated. The vaso-motor spasm as shown by the blanching of mucous membranes after its topical application is probably a purely local action. There is no convincing evidence that when given internally it has any direct action upon the arterial muscles. Concerning the pulse-rate, there is much divergence of statement. According to Reichert, a very small dose of cocaine decreases the rate by stimulation of the cardio-inhibitory centre, moderate doses increase the rate by depressing these centres and in some cases also the intrinsic inhibitory mechanism, while large doses may finally slow the heart by the action upon the motor ganglia.

The experiments of Danini, of Berthold, and of Reichert are concordant in showing that after section of the spinal cord alone, or of the spinal cord and the vagi, cocaine does not distinctly increase the arterial pressure,—proof that the chief cause of the rise of the arterial pressure under the influence of cocaine is centric vaso-motor spasm.

As showing the stimulant action of the small dose of cocaine on the heart, Mosso and H. G. Beyer, as the result of their experimental studies, made in the one case on the cut-out frog's heart, in the other upon the isolated heart of the terrapin, found that the minute dose of the alkaloid increased the whole amount of force put out by the heart, as well as the power of the individual systolic contraction; while Pachon and Moulinier, in experiments with cocaine on the heart of the frog *in situ*, find that after a moderate dose of cocaine there is a hypertonicity of the heart due to a direct action upon the muscular fibres. Observers affirm that the heart of the mammal is arrested by the toxic dose in diastole, which is in accord with the statements of Von Anrep and Nikolsky concerning the heart of the frog and of H. G. Beyer concerning that of the terrapin, diastolic arrest being affirmed by all these investigators. Pachon and Moulinier declare that the ventricles are arrested in systole, the auricles in diastole. According to these investigators, the arrhythmia of advanced cocaine-poisoning is really a rhythm which differs from the normal in that the contractions occur in regular groups; later there is a dissociation of the auricular and ventricular rhythms.

The action on the vessels is uncertain. Mosso found that when he experimented with artificial circulation upon extirpated kidneys small doses of cocaine had no sensible effect upon the blood-vessels; and Durdafi states that marked narrowing of the vessels of the rabbit's ear can be seen when cocaine is injected, but is prevented by previous section of the sympathetic. Contrariwise, H. G. Beyer found in experiments upon the terrapin that both large and small doses of cocaine produce contraction of the blood-vessels by a direct influence; and Laffont experimentally reached the conclusion that one of the chief actions of cocaine is to contract the blood-vessels by affecting the nerve-endings in their walls.

The results of the studies made by various investigators with the direct application of cocaine to the heart lead to the conclusion that while small doses of the alkaloid feebly stimulate the viscous, toxic doses act as a depressant and finally as a paralyzant; that cardiac depression is one of the causes of low arterial pressure in advanced cocaine-poisoning is further evidenced by the rapid and immediate fall in the pressure which occurs when cocaine is injected into a dog whose spinal cord has been cut and vaso-motor system paralyzed.\* The opinion of Reichert, that widening of the blood-paths by vaso-motor paralysis is the most important factor in the causation of lowered blood-pressure in advanced cocaine-poisoning, seems to be so far correct that the probabilities are that such widening of the blood-paths occurs.

The testimony as to the action of the alkaloid upon the pulse-rate and upon the inhibitory nerves of the heart is so various that no positive conclusions are warranted without further study.

Von Anrep states that the pulse-rate is usually increased, but that this increase is not marked in rabbits, while in Ott's experiments upon dogs the pulse usually becomes slower. Von Anrep also states that the vagi are paralyzed by large doses of cocaine, while Ott, Nikolsky, Laffont, and Durdafi declare that it does not affect the vagi, and Berthold states that previous section of the vagi has no effect upon the course of the symptoms caused by cocaine.

Reichert found in an elaborate series of studies that "very small doses of cocaine decrease the rate by stimulating the cardio-inhibitory centres; small to moderate doses increase the rate by depressing these centres, and in some cases by depressing also the cardio-inhibitory ganglion; large doses cause a transient decrease, followed by a rise or a permanent decrease, the decrease being due to a depression of the accelerator or motor ganglion in the heart, and the increase to the factors before mentioned. The cardio-inhibitory centres are invariably affected, being primarily stimulated and secondarily depressed."

*Muscles.*—Although there is some contradiction of evidence, yet it would appear established that cocaine is a direct muscle poison, at first stimulating and in large doses afterwards paralyzing. These effects are, however, probably too slight to be demonstrable in warm-blooded animals.

Alms, Nikolsky, and B. von Anrep state that the striated muscles are not affected by the alkaloid, while Ott affirms that it acts upon them like veratrine and is confirmed in this by Buchheim and Eisenmenger. The tracings given by Ott would appear to prove that the muscular contraction is prolonged by cocaine, and can hardly be accounted for by a condition which M. J. Rossbach and B. von Anrep allege to be produced,—viz., a peculiar sensibility of the muscle similar to that produced by curare, and, like it, caused by a lessening of muscle-tonus by paralysis of the peripheral nerve-endings.

In the ergographic experiments of Benedicenti cocaine both heightened muscular energy and increased resistance to fatigue,† while Mosso found that in man, when the muscles were exhausted by work and fasting, the exhibition of cocaine in the dose of a grain and a half more than doubled the response to stimuli. These experiments throw a peculiar light upon the assertions of travellers, that cocaine in the South American Indians enormously increases the power of withstanding fatigue. The present difficulty in the way of the full acceptance of the natural deductions from them is the fact that in America and in Europe cocaine has appeared to fail as a stimulant during fatiguing labors.

*Temperature.*—The rise of rectal temperature in cocaine-poisoning sometimes amounts to as much as 8° F. It is certainly not due to the

\* See experiments of I. Ott, *Toxicological Studies*, 1874, 30.

† Sobieranski believes, however, that the effect of cocaine is through the nerve-centres (see *Gazeta Lekarska*, 1896, No. 4).

convulsions, as it usually occurs before the motor disturbance.\* In fatal cases it is followed by a fall, so that before death the temperature may become subnormal. In the calorimetrical experiments of Reichert the rise of temperature was found to be due to a great increase in the heat production.

Reichert has further determined that after section of the spinal cord† at its junction with the medulla, as well as after section of the *crura cerebri*, cocaine is powerless to produce rise of the temperature, and therefore concludes that the rise of temperature produced by cocaine is of cerebral origin, and is due to stimulation of the thermogenic centres in the caudate nucleus and to motor excitement produced by stimulation of the cortical motor centres.

*Urinary Secretion.*—Such varying results have been recorded by clinicians as to the effect of cocaine upon the amount of urinary secretion that its action is probably not constant. According to Bignon, the single large dose may produce an anuria so prolonged as to bring on uremic symptoms. There is some reason for believing that cocaine reduces the nitrogenous elimination, but the experiments upon the subject are hardly sufficient to warrant the positive conclusion that the alkaloid checks protoplasmic waste.

I. Ott and Atherton P. Mason have found that when cocaine is taken habitually it not only lessens the urinary secretion but also markedly decreases the elimination of urea, while in three experiments Richard Fleischer determined that the alkaloid markedly reduces nitrogenous elimination. Mason experimented with very large therapeutic doses of cocaine taken during prolonged exercise, and states that his results were contrary to those previously reached by Gazeau.

In Ott's experiments the urine, under the influence of cocaine, became full of calcium oxalates. Sugar and albumin have been frequently noted in the urine of poisoned animals, but Von Anrep affirms that their presence is due to the prolonged asphyxia induced by the drug.

*Eye.*—When locally applied about the eye cocaine produces a dilatation of the pupil which from a four-per-cent. solution reaches its maximum in about an hour and disappears in from twelve to twenty-four hours. The dilated pupil is to some extent responsive to light and accommodation and can be further dilated by atropine or contracted by physostigmine.

The dilatation is certainly due at least in part, perhaps solely, to the stimulation of the sympathetic (dilator) nerve-endings. The fact that physostigmine is capable of contracting the pupil would indicate that the oculo-motor system is not entirely paralyzed, and the increase in dilatation produced by atropine suggests also the same conclusion.

The experiments of Nikolsky, Holtzke, Limbourg, as well as of Schöler and Pflüger (quoted by Limbourg), show that cocaine applied to the eye immediately after section of the sympathetic does dilate the pupil, although later, when suffi-

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\* P. Langlois and Charles Richet have found that the temperature of the cocainized animal has a great effect in determining the amount of cocaine necessary to produce convulsions. The higher the temperature the smaller the dose necessary, and when the animal was kept at a temperature of 39° C., only tonic convulsions were produced.

† The rise of temperature which has been noted by Mosso after section of the spinal cord may have been the result of imperfect division.



cient time has elapsed for degeneration of the sympathetic fibres to occur, the alkaloid is powerless. This would appear to prove that cocaine dilates the pupil by stimulating the sympathetic nerve-endings; but, according to Schultz, very strong solutions of cocaine will dilate the pupil after nerve degeneration has occurred, though weaker solutions fail to act. Further, Schultz found that when, in the cat, he extirpated the superior cervical ganglion on one side, waited a sufficient length of time for degeneration of the dilator nerves, and then applied cocaine to both eyes, he obtained a maximal dilatation on the unoperated side, but a medium dilatation on the operated side. Allowing the correctness of Schultz's experiments, the double action of cocaine appears to be demonstrated. Limbourg states that electrical irritation of the cornea may restore to such an eye the power of responding to cocaine.

✶ *Respiration.*—Small doses of cocaine increase distinctly the rapidity of the respiration, and in some cases also the depth (Von Anrep, Mosso, Danini, Ott, and Nikolsky). After toxic doses the respirations become at first rapid and more shallow, then irregular with interruptions, after each of which the respiratory movements begin deep and slow, but become more rapid and shallow until the next stand-still. As Mosso found that after section of the vagi cocaine causes an enormous increase of the rapidity of the breathing and at the same time so modifies the rhythm that expiration is no longer quicker than inspiration, it must be considered that the drug acts directly upon the respiratory nerve-centres as a respiratory stimulant. The first stimulant effect of cocaine upon the respiratory centres appears to be followed after fatal doses by a paralyzing influence which leads to death from asphyxia.

*Intestines.*—According to Von Anrep, the intestinal peristalsis is markedly increased by moderate doses. After large doses this increase is followed by great sluggishness deepening into paralysis. Tarchanoff states that coca increases the mucous secretions, but Von Anrep affirms that it decreases them.\*

**SUMMARY.**—Cocaine is a primary stimulant, and in toxic quantities secondarily depressant to the brain and spinal cord. When locally applied it is a paralyzant to peripheral nerves, acting much more powerfully on sensory than on motor nerves. In moderate doses it is stimulant, in overdose depressant, to the vaso-motor centres. Upon the heart itself the moderate dose of the alkaloid acts primarily as a stimulant, increasing to a slight extent the amount of force put forth by the heart; in toxic quantities it lessens the heart action. There is also reason for believing that cocaine exerts a direct influence upon the coats of the blood-vessels, which is, however, so feeble as not to be of practical importance except when the cocaine is applied locally. Upon striated muscles cocaine appears to have a peculiar though very feeble action, which is not manifested during poisoning by it. Upon the eye cocaine acts as a mydriatic. It is a powerful stimulant to the respiratory centres, increasing the rapidity and fulness of the respirations, but if the dose

\* M. E. Gley states (*Compt.-Rend. Soc. Biol.*, iii, 560) that when cocaine is injected into the portal vein it produces comparatively little effect, and he believes that it is destroyed in the liver. This is criticised by Chouppe (*Ibid.*).

be sufficiently large it after a time causes the respirations to become very shallow, and finally paralyzes the respiratory centres. Moderate doses are said to increase, large doses to paralyze, peristalsis.

**Therapeutics.**—Locally cocaine is largely used for its anesthetic influence (see page 51). It is also of value as a topical remedy by virtue of its action in constricting the blood-vessels. In acute *coryza* a ten-per-cent. solution applied to the nostrils will sometimes afford permanent relief, but a combination of a four-per-cent. solution with bismuth (three drachms to the ounce of mucilage) is more generally useful. It should be applied by means of a dropper every three or four hours. In *hay fever*, in the peculiar irritated sore throat of advanced *phthisis*, in chronic *laryngitis*, in *inflamed hemorrhoids*, in *fissure of the anus*, and even in open *cancer* its application will often afford temporary relief. In some cases of *dysentery* with excessive nervous irritability of the rectum, cocaine suppositories are of great service. Cocaine is also sometimes useful as a local hemostatic in arresting *nasal* and other mucous membrane *hemorrhages*.

For local use the two- to ten-per-cent. solution may be employed, care being exercised not to use a possibly fatal dose of the drug.

As an internal medicament cocaine is useful as a respiratory and circulatory stimulant and as a tonic. It is largely used in the same class of cases in which strychnine is found to be available. Less powerful in its influence than is strychnine, it is especially useful as an aid to that alkaloid. (See *Respiratory Stimulants*.) Its stimulant influence upon the cerebrum naturally led to the expectation that it would be of value in cases of depression of spirits and even of true *melancholia*. The results of our own experience, after thorough trial, however, are in accord with the generally expressed opinions of alienists, that it has no remedial value in any form of mental aberration. Sometimes it appears to produce at first a temporary relief, but this does not continue; and if the remedy be pushed, anorexia, restlessness, or other disagreeable symptoms usually demand its withdrawal. In *neurasthenia* and *hysteria* it is valuable only as a stimulant and stomachic, acting better in the form of the fluidextract than cocaine itself; and in all these cases there is especially the danger of the formation of the cocaine habit. Large doses of the fluidextract are sometimes of service.

In the form of large doses of the fluidextract, coca has appeared to us to be of service during the breaking off of the *opium habit*, exerting some stimulant influence upon the nervous system, and restraining the tendency to diarrhœa and loss of appetite; care must be taken, however, not to substitute a new habit fully as pernicious as the old one. Some European clinicians have found cocaine of service in the treatment of *serous diarrhœas*. It is undoubtedly of value for the relief of *excessive vomiting*, especially when due to gastric irritation. Thomas D. Dunn states that hypodermic injections of one grain control the pain of *migraine*. Aschenbraidt asserted that, in doses

of 0.15 grain, cocaine was a valuable stimulant during forced marches; but in a series of careful trials with it by the medical rowing crew of the University of Pennsylvania it appeared to have no value, and the general experience seems to conform with this result.

**Toxicology.**—The symptoms which have been present in cocaine-poisoning, or have been produced by the coca-leaf or its preparations, in the United States or in Europe, differ essentially from the descriptions of those said to be caused by the plant in the South American natives.\* We believe that in no recorded cases has there been anything resembling the beatific visions and exhilarations described by Montegazza. Ordinarily, in the mildest cases of poisoning with us, there are great restlessness and nervous excitement, but no sense of beatitude; rather a condition of terror. With this state come usually distinctly accelerated pulse, increased frequency of respiration, and, perchance, muscular twitchings or even mild convulsions. In the more severe cases of poisoning the symptoms vary; sometimes there have been nausea, vomiting, rapid, almost imperceptible pulse, great perspiration, and collapse with or without loss of consciousness; in other cases the pulse has been slow and feeble, and sometimes pronounced cyanosis, with slow or almost arrested respiration, has been the most alarming manifestation. The pupils are usually dilated, but have been reported in some cases as "contracted." After very large doses convulsions usually occur; they are often violent and epileptiform; not rarely, at times, at least, they are partial, and in many cases opisthotonos has been pronounced. Consciousness rarely escapes; usually it is simply lost, but sometimes it is merged into a mania with hallucinations and delusions, which mania may become violent and even homicidal, as in a case reported by Mattison.

The number of cases of poisoning by cocaine is very great, and although large doses have been recovered from, excessively violent symptoms have followed the use of smaller amounts. It is remarkable, also, that in many of these cases the drug has been employed for a local effect.

The fatal cases, to the details of which we have had access, are those reported by Kolomnin, twenty-four grains into the rectum for local anesthesia; F. M. Thomas, four-per-cent. solution used locally for toothache, in unknown quantity; Knabe, four-per-cent. solution, twelve drops given hypodermically to a girl of eleven years, death in forty seconds (for details, see J. B. Mattison); J. H. C. Simes, one drachm of twenty-per-cent. solution injected into the urethra, followed immediately by violent convulsions, ending in death in twenty minutes, autopsy proved that urethra was not ruptured. Half an ounce of a two-per-cent. solution of cocaine injected into hydrocele and allowed to stay about a minute is said to have caused death (Paul Berger). O. H. Garland, death said to have been due to the application of twenty drops of a five-per-cent. solution to the gum. E. Pfister, death from an unknown quantity of a twenty-per-cent. cocaine solution injected into the urethra.

Some of the most remarkable cases of poisoning by small quantities are those reported by T. H. Burchard, ten drops of a four-per-cent. solution injected hypo-

\* The belief of H. H. Rusby, that these differences depend upon alterations of the coca-leaf during its drying and transmission across the seas, has hardly been sustained (*Therap. Gaz.*, 1888).



dermically caused unconsciousness and apparent death in four minutes; Myerhausen, eight drops of a two-per-cent. solution upon the conjunctiva produced in a girl of twelve years violent symptoms; George T. Stevens, one in which four minims of a three- and a half-per-cent. solution, given to a strong man, produced violent convulsions, followed by mania; Grosholz, three drops of a four-per-cent. solution in the eye; Frost, one drop of a one-per-cent. solution in the eye produced in a child of fourteen marked poisoning; Ramsden Wood reports violent poisoning with four minims of a twenty-per-cent. solution. A number of cases are on record in which very severe symptoms have been produced by one grain given hypodermically (see Mattison, Addinsell, and Pitts); and it is plain that, although this dose has been used to a considerable extent, its employment is unjustifiable. The occasional effects of the local application of cocaine are very remarkable.\*

On the other hand, large amounts of the drug have been recovered from.

Von Ploss reports twenty-two grains taken by an apothecary, by the stomach, with spontaneous recovery, although the urine was suppressed for twenty-four hours. In another case ten grains taken hypodermically in the course of five hours produced complete unconsciousness, excessive failure of circulation, slow respiration, recovery under treatment (J. S. Spear); E. Caldwell reports recovery after the hypodermic injection of five grains, which produced convulsions with asphyxia. A case reported by W. Finlay is interesting, because six grains given hypodermically to a pregnant woman lowered the pulse to 38 and the breathing to 5, but did not cause a miscarriage.

It is not safe to put upon mucous membranes amounts which if given hypodermically would be dangerous; so that not more than three-quarters of a grain should be used locally.

The *treatment* of cocaine-poisoning must be largely symptomatic. When there is great cerebral and motor excitement, we have found chloroform to act very happily. Partial anesthesia may be maintained for some moments. If the symptoms do not yield to such medication, chloral may be cautiously exhibited. When the toxic manifestations are syncopal, hypodermic injections of digitalis may be given, while alcohol and ammonia are exhibited by the mouth. In some cases life has been apparently saved by artificial respiration. Intravenous injection of salt solution has been recommended.†

Cases of *cocainismus* or chronic cocaine habit are not rare, but in the great majority of instances the victim is addicted to the use of more than one narcotic. Usually the cocaine has been taken as a substitute for, or aid to, morphine: in a number of cases the habit has been formed by the local use of the drug for hay fever. The symptoms are in no way characteristic; dreaminess, apparent inability to attend to the ordinary duties of life, loss of reliability, promptness, and punctuality, varying mental aberration suggesting, but different from, that of paranoia, occurring in any case, should arouse suspicion. The paranoiac, unless greatly depressed, is usually egotistical, self-reliant, conceited; the victim of cocainism, in matters not connected with his habit, is usually even less self-assertive and more easily led

\* In addition to cases mentioned, see *Brit. Med. Journ.*, Nov. 1885; *Deutsch. Med. Wochensh.*, No. 46, 1886; *New York Med. Rec.*, 1886, ii.; *La Pratique Méd.*, Jan. 1891; *S. J.*, cclvii. 201.

† *Systemic Lavage for Poisons*.—Intravenous injection of normal saline solution as a treatment for acute poisoning has been experimented upon by Carlo Bozza (*Canadian Pract.*, 1898, xxiii.), who believes that it leads to rapid elimination and slow absorption, owing to fulness of the blood-vessels. He determined that the minimum fatal dose of cocaine given to dogs hypodermically is 0.025 gramme per kilo; rising to 0.03 if hypodermoclysis is employed, and to 0.035 with lavage of the organism.

than the normal individual. Magnam affirms that a peculiar hallucination as to the existence of foreign bodies under the skin is characteristic.

The will and the desire to reform are as weak as in the opium habit, and the greatest difficulty is usually to get the victim earnestly to desire reformation. The abrupt withdrawal of the narcotic is probably always safe; thus, in a case in which fifteen grains were taken hypodermically daily, the immediate cessation of exhibition was followed by no greater disturbance than diarrhœa, dyspepsia, and nervous depression, which subsided in the course of two or three days. (For cases, see Grundlach and Mattison.)

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## FAMILY V.—EXCITO-MOTORS.

IN this class are included such drugs as increase the reflex activity of the spinal centres, and thereby give rise to disturbance of motility. The only representatives of the class used by the practitioner of medicine are those drugs which contain strychnine as their active principle.

### NUX VOMICA.

The seeds of *Strychnos Nux-vomica*, a middle-sized tree growing in the East Indies and Australia, whence the drug enters commerce. The fruit of the nux-vomica tree resembles externally the orange. Each fruit contains four or five seeds. These are circular, nearly flat disks, a little less than an inch in diameter, covered with very short, satin-like, grayish hairs; internally they are tough and horny, and are possessed of an intensely bitter taste. The effects of nux vomica are due chiefly to the alkaloid *strychnine*—of which it should contain not less than one and a quarter per cent., although it contains another alkaloid of physiological activity, *brucine*. These alkaloids exist in combination with an acid, the so-called *igasuric* of Pelletier and Caventou, which, according to Husemann, is identical with malic acid. It is usually estimated that strychnine constitutes about forty per cent. of the alkaloids. Practically there is no qualitative difference between the medical action of strychnine and that of the cruder preparations of nux vomica, over which it usually should have the preference on account of definiteness of action.

As kept in the shops, *strychnine* is a grayish-white powder, but may be obtained in octahedral or quadrilateral prisms. It is so bitter that it will impart a very intense bitter taste to seven hundred thousand times its weight of water. On account of its insolubility (one in about three thousand parts of cold water) it is very rarely used in medicine, at least in the United States, the sulphate being universally preferred, and being what is commonly meant in American writings when the word “strychnine” is used. Strychnine sulphate contains about seventy-five per cent. of strychnine.

#### Official Preparations :

Extractum Nucis Vomicae (5 per cent. of

Strychnine) .....  $\frac{1}{4}$  to  $\frac{1}{2}$  grain (0.015–0.03 Gm.).

Fluidextractum Nucis Vomicae ..... 1 to 3 minims (0.06–0.18 C.c.).

Tinctura Nucis Vomicae (0.1 per cent.

Strychnine) ..... 10 to 30 minims (0.6–2.0 C.c.).

Strychnina .....  $\frac{1}{60}$  to  $\frac{1}{20}$  grain (1–3 Milligm.).

Strychninae Sulphas .....  $\frac{1}{60}$  to  $\frac{1}{20}$  grain (1–3 Milligm.).

Strychninae Nitræs .....  $\frac{1}{60}$  to  $\frac{1}{20}$  grain (1–3 Milligm.).

**Local Action.**—The local action of strychnine is that of a very feeble irritant; upon the mucous membrane of the stomach it acts like a simple bitter.

**Absorption and Elimination.**—Strychnine is absorbed rapidly, whether taken by the mouth or by hypodermic injection.

Several investigators have attempted to determine the comparative rate of absorption of strychnine in different portions of the alimentary canal by isolating these different portions by ligatures and then injecting strychnine into them. After tying the pylorus, Bouley and Colin found that the absorption of strychnine was rapid in the stomachs of dogs and cats, while Tappeiner determined that in cats it was taken up very slowly. In two series of experiments, S. J. Meltzer found that, after tying the cardiac and pyloric ends of the stomach, large doses of strychnine would remain in the stomach of the rabbit without producing any physiological effect, while under similar circumstances in the dog the gastric absorption was extremely slow and uncertain. It is rapidly absorbed in the small intestine.

Strychnine has been detected by chemists in the blood, kidney, liver, heart, brain, spinal cord; indeed, practically in all portions of the system. The statement of R. W. Lovett, that it accumulates in the spinal cord, has been disproved by Ipsen and by Lesser.

Strychnine is eliminated promptly, having been detected in the urine five minutes after its absorption, and others have detected it in the urine half an hour after its exhibition; and in various poisoning cases, fatal within two hours, it has been found in the urine. Kratter and Mann believe that they have proved that the elimination is complete within forty-eight hours.\* It escapes from the body to some extent unchanged, as it has been found in the urine by Peter von Rautenfeld, by Wormley, by Schauenstein, and by Kratter. According to P. C. Plugge, a portion of the alkaloid is converted into *strychnic acid*.†

**Physiological Action.**—According to the experiments of Borzi, strychnine affects vegetable protoplasm. Upon all animals strychnine probably acts similarly, but with great variations of power.

According to Leube, it takes ten times as much strychnine to kill chickens as it does to kill other birds, weight for weight; and among mammals the guinea-pig is very insensitive to it. It has also been asserted that on some monkeys it has but little influence (*Boston Med. and Surg. Journ.*, 1872). Very young animals are said to be quite insensitive to it.‡ The resistance of birds to the poison is attributed by Falck partially to slow absorption and partially to a destruction of the poison in the body.

The characteristic symptom produced by the toxic dose of strychnine is violent convulsion in which all the muscles of the body are involved, which may endure until death from asphyxia, the spasm of the muscle of the chest preventing respiration. We have seen

\* Schiff and Lautenbach believe that they have proved that the alkaloid is destroyed, at least in part, in the liver; a conclusion which is strongly combated by Chouppe and Pinet (*Compt.-Rend. Soc. Biol.*, 1887, cv.), and is very doubtful.

† The theory that strychnine becomes fixed in certain tissues of the body, originally proposed by Widal and Nobécourt, has received considerable credence, but its correctness has certainly not been proven. For discussion of the whole subject, with experiments and literature, see paper of S. J. Meltzer and G. Langmann.

‡ See *Arch. f. Ges. Physiol.*, 1884, xxiv. 530; also Behrend Lau (*Elmshorn Inaug. Diss.*, 1886).

death occur in the first convulsion in animals; but Tardieu states that he knows of no such instance in man (compare case of Demme). After a time the paroxysm is at an end, the jaw drops, the muscles relax, and a period of calm comes on, to be succeeded by a second convulsion like the first. These convulsions are excited by the slightest touch, by a draught or breath of air, even by a loud sound; but a firm grasp or hard rubbing of the muscles is frequently grateful. A slight rigidity is sometimes manifest between the paroxysms, but no marked stiffness.

*Cerebrum.*—So far as our present knowledge goes, strychnine has little or no influence upon the cerebral cortical centres. The stimulation of the special senses sometimes seen in the beginning of strychnine-poisoning is probably, though not certainly, peripheral in its origin; consciousness is probably never directly affected by the drug.

*Spinal Cord.*—The spinal origin of the convulsions of strychnine was first demonstrated by Magendie in what was probably the earliest pharmacological study leading to the therapeutic use of a drug, and has been confirmed by a large number of experimenters. After the administration of the drug, even in doses too small to give rise to convulsions, the reflexes are greatly exaggerated. The spasms occur after section of the spinal cord below the point of division.

It has been proved by Van Deen, by Valentin, and by A. J. Spence that when strychnine is placed upon the cut upper surface of the brain or spinal cord so that it will diffuse itself within the spinal cord without being carried by the circulation, convulsions appear in those muscles whose nerves have their origin near the point of application, and spread from muscle to muscle as the poison creeps through the cord. The accuracy of the statement of Claude Bernard, that when all the posterior nerve-roots are cut no convulsions occur, whereas, if a single afferent root remains, irritation of its nerve will cause general tetanic spasm, has been denied by Spitzka, but is probably correct. If so, it demonstrates that the reflex motor ganglionic cells are incapable of originating an impulse, and in strychnine-poisoning are simply in such a condition of over-excitability as renders them exceedingly sensitive to slight irritations and causes them to respond most energetically to the feeblest stimulus, the convulsion always being therefore a reflex phenomenon.

Whether the action of the alkaloid is upon the sensory or upon motor ganglia of the spinal cord is not yet definitely proven. The observations of Spence would seem to indicate that it is the sensory apparatus which is excited. This investigator found that after its local application to the upper part of the spinal cord, as the poison travelled down the cord there was a time when irritation of the fore feet caused only spasm in them; later in the experiment, irritation of the front feet caused spasm of both the front and hind feet, although irritation of the latter did not produce other than normal reflex movements; later still in the poisoning came a stage when irritation of the front legs was powerless to cause spasm in the hind legs, although irritation of the latter would now cause spasm in the former. Bier-nacki believes that the cortical portion of the pyramidal or motor tract does not share in the stimulation, because he has found that in the strychnized rabbit the psycho-motor centres in the brain are even less susceptible to stimulation than in the normal animal.

On the other hand evidence that the effect is on the motor apparatus is furnished by the experiments of Van Deen, who so divided all the tissues that the anterior portion of an eviscerated frog was connected with the posterior solely by the posterior columns of the cord. When one or two drops of a solution of strychnine were placed in the mouth of the prepared batrachian, tetanus, confined to the



anterior segment of the body, was developed; and it was also found that while irritation of the posterior feet caused in them only ordinary reflex movements, in the front legs tetanic spasms were simultaneously induced.

Strychnine is evidently a powerful stimulant to the motor cells of the whole spinal tract up to the pons Varolii. Hare found demonstrable histological changes in the cells of the anterior cornua.

*Motor Nerves.*—After death from strychnine, the functions of the motor nerves are always found to be more or less impaired, so that galvanization of the nerve-trunk produces either very feeble contractions in the tributary muscles or none at all.\*

Although this paralysis of the motor nerves may be, in part, due to the exhaustion produced by the excessive number of violent impulses which travel along the motor nerves during the period of strychnic convulsions, the drug exercises a direct depressant action on the motor end plates.

Kölliker found that when he cut the sciatic nerve in the frog and exhibited strychnine the divided nerve would respond to galvanic stimulation after all functional power had been lost in the nerve whose connection with the centres was intact. These experiments have been confirmed by Martin-Magron and Buisson, and must be accepted. On the other hand, it has been shown by Vulpian, by E. Poulson, by C. G. Sautesson, and others, that when the nerve has been divided, as in the experiments of Kölliker, it finally becomes paralyzed in strychnine-poisoning; and Vulpian has found that if the doses have been properly adjusted the motor nerve after a time will regain in the poisoned frog its activity before stimulation of the spinal cord has altogether passed off, so that the history of such an experiment is, first, tetanus,—then paralysis, due to the loss of power by the nerve-trunks,—and then again a tetanus which gradually subsides into the normal condition. Further, as pointed out by Richet, and as we have frequently seen, if an enormous dose of strychnine be injected into the jugular veins of the dog, death immediately results practically without convulsion. Under these circumstances the motor nerves will be found to have entirely lost their power of responding to galvanic or other stimulation, although they may still be able to transmit sufficient efferent impulses from the spinal cord to produce slight but distinct choreic muscular contractions.

*Sensory Nerves.*—The afferent or sensory nerves appear not to be affected by strychnine. Martin-Magron and Buisson having tied all the tissues of a hind leg of a frog except the nerve, and injected strychnine into the body of the batrachian, found that at a time when convulsions had ceased in all portions of the body except the leg to whose nerve the poison had not had access, slight irritation of the poisoned foot would induce tetanic spasms in the protected leg, thus showing that though the motor nerves to which the strychnine had had access were completely paralyzed, the afferent nerves were still functionally active.

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\* See Matteucci (*Traité des Phénomènes électro-physiologiques*, Paris, 1844), Moreau (*Comptes-Rendus Soc. de Biol.*, 1855), M. Ambrosoli (*Gazette Médicale*, 1857, 525), Wittich (*Bericht d. Fortschritte d. Anat.*, 1857, 434), Kölliker (*Virchow's Archiv*, 1856, x, 239), and Vulpian (*Archives de Physiologie*, Nov. 1870, 125). The statement of W. H. Klapp, that he has found in thirty-seven experiments the motor nerve unimpaired in the frog after death from strychnine (*Journ. Ment. and Nerv. Dis.*, Oct. 1878), may depend upon the fact that in some species of frogs the nerves are extraordinarily refractory to the action of strychnine, or it may be that he employed such powerful stimuli that all apparent differences were lost. Sautesson found that strychnine acts twelve times more powerfully upon the nerves of *Rana esculenta* than upon those of *R. temporaria*. S. Leduc believes that he has demonstrated that strychnine can be electrolytically carried into a human nerve and temporarily suspend its functional power (*C. R. S. B.*, 1902, liv.).

*Circulation.*—The full dose of strychnine produces a rise of the arterial pressure which is enormously increased during the convulsion, after which there is a very pronounced fall in the arterial pressure.\* The primary rise is not due to the convulsion, since it precedes the convulsion, and occurs in curarized animals. It is largely due to vaso-motor contraction, since Mayer, Klapp, and Reichert have all found that after paralysis of the dominant vaso-motor centres by

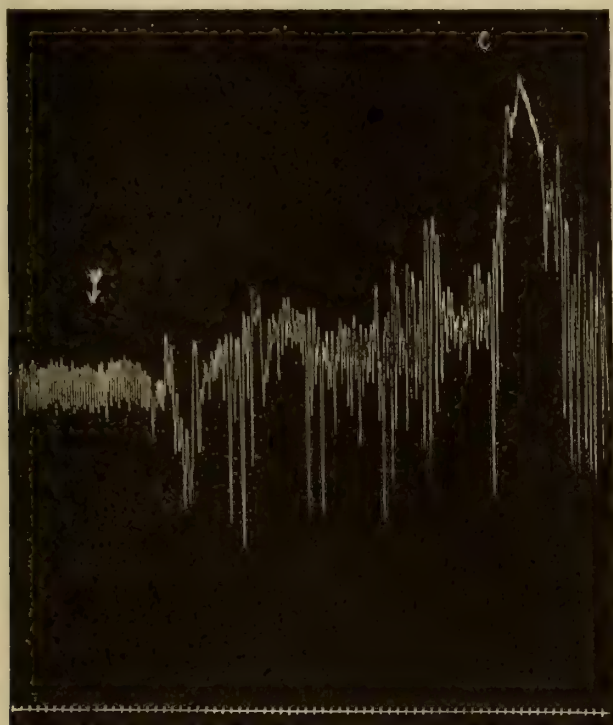


FIG. 9.—SHOWING THE EFFECT OF STRYCHNINE ON THE CIRCULATION BEFORE AND DURING THE CONVULSIVE PERIOD.

The strychnine was injected at the point marked with an arrow; at C a convulsion occurred. Time marker indicates 2 seconds.

section of the cord, strychnine causes no rise at all,† or an exceedingly slight one, of the arterial pressure. The fall of the arterial pressure has been shown by Klapp and Reichert to be due, in part at least, to paralysis of the vaso-motor centres. By the intravenous use of very large doses of strychnine it is possible to produce immediate paralysis of those centres, with corresponding fall of the arterial pressure.

\* See also Richter (*Zeitschrift f. ration. Med.*, 1863, xviii.), Denys (*Arch. f. Exper. Path. Pharm.*, xx. 306), Kionka (*Arch. de Pharmacod. internat.*, 1898, v.).

† Schlesinger (*loc. cit.*) found after the division of the cord that the rise of arterial pressure caused by strychnine both absolutely and relatively exceeds that produced in the normal animal. This result we believe to have been due to imperfect section of the cord. For an elaboration of the reasons for this belief, see tenth edition of this treatise.

Our knowledge of the cardiac action of strychnine is still imperfect. Although Lahousse believes that in any dose strychnine depresses the intra-cardiac ganglia, it is probable that the small dose has a stimulating influence upon the heart. Igersheimer found that it slowed the rate but increased the volume of the wave in the isolated heart of either the frog or rabbit, but Kakowski, while he noted the slowing, failed to obtain any evidence of increased power.

In regard to the action of the alkaloid upon the vagi there is much difference of statement by investigators. Carl Heinemann, Mayer and Klapp all affirm that the heart under the influence of strychnine can be arrested by galvanization of the par vagum, but Martin-Magron and Buisson, E. T. Reichert and Lahousse, state that the sufficient dose of strychnine paralyzes inhibition.\* Reichert has found that the early effect of strychnine is to stimulate the peripheral inhibitory apparatus of the heart, but that if the dose has been sufficient this stimulation is followed by pronounced depression or even complete paralysis.†

*Blood.*—Harley found that blood shaken for twenty-four hours with air contained 11.33 parts of oxygen and 5.96 parts of carbonic acid; while blood treated in a precisely similar manner, except in the addition of strychnine, yielded 17.80 parts of oxygen and 2.73 parts of carbonic acid. Kionka found that blood taken from the strychnized animal does not absorb oxygen with the avidity of normal blood, although no spectroscopic changes could be discovered in it. Moreover, his analysis of blood gases shows during the dyspnœic stage of the poisoning an extreme lack of oxygen without any excess of carbonic acid. Maurel states that five centigrammes of strychnine sulphate are sufficient immediately to kill the leucocytes in one hundred grammes of blood, and that in poisoning by strychnine sulphate the leucocytes and the animals die at the same time.

*Respiration.*—The injection of strychnine produced in the dog an extraordinary increase in the respiratory air-movement, which in H. C. Wood's experiments never amounted to less than seventy-five per cent., and sometimes rose to three hundred per cent. On chloralized dogs the respiratory effects of the alkaloid were even more pronounced.

Strychnine is among the most certain of the respiratory stimulants, its action upon the respiratory centres being evidently a portion of its wider influence upon the whole motor tract.

*Temperature.*—We know of no recorded temperature-curve in human poisoning, but in the lower animals there is usually a primary elevation of the temperature followed by a pronounced fall, both the rise and fall apparently being in greater or less measure independent of the convulsions.

\* For the paper of Brunton and Cash showing that strychnine increases the "refractory period" of the isolated frog's heart, see *Proc. Roy. Soc.*, 1883. A consideration of this memoir would require an elaborate discussion of the minute points of cardiac physiology, and, as it would throw at present no light upon the practical use of the drug, is not entered upon.

† Reichert determined that five milligrammes of strychnine per kilogramme of weight will paralyze the peripheral vagi in the dog.



According to the experiments of Kionka, during both temperature periods, heat-production, and heat-dissipation are above the normal, but during the rise of temperature the increase in heat-production is greater than the increase of heat-dissipation, while during the period of falling temperature the overplus of heat-dissipation is greater than that of heat-production. Harnack confirms the results of Kionka, but has found also that irregularly at any time during the poisoning there may be a sudden arrest of heat-production without corresponding fall in heat-dissipation, so that the temperature of the animal rapidly descends. Anton Obermeier has found that in the rabbit strychnine causes a notable increase in the production of carbonic acid,—*i.e.*, of oxidation; and U. Mosso\* affirms that even in the curarized dog a very pronounced rise of rectal temperature may be produced by strychnine. The final fall of temperature is due to the excessive dissipation of heat, which in turn is probably the outcome of vaso-motor paralysis.

It would appear that the action of strychnine upon heat-production and heat-dissipation is independent of its convulsive influence, and is probably the outcome of some effect upon the central nerve-system, but we have not sufficient evidence to determinate the exact nature of this influence.

*Eye.*—The effect of strychnine upon the normal eye has been studied by Von Hippel and Cohn, with rather different results. They both, however, found the sharpness of vision increased.

**SUMMARY.**—Strychnine has no effect on the cerebrum but is a powerful stimulant to the spinal cord. Toxic doses produce violent reflex tetanic convulsions, without loss of consciousness, by causing such excessive irritability and excitement of the ganglionic spinal cells that these cells respond overwhelmingly to the slightest stimuli; they also lower the functional activity of the motor nerve-trunks by producing exhaustion and by a direct paralytic influence. It increases the blood-pressure by stimulating the vaso-motor centre and perhaps also by an action directly on the heart. There is also reason for believing that the toxic dose paralyzes the peripheral pneumogastric nerve and greatly depresses the heart itself and the vaso-motor system. The ozonizing power of the red blood-corpuscles appears to be lessened by toxic doses of strychnine. The absorption and the elimination of strychnine are rapid, the alkaloid escaping partly in the form of strychnic acid and partly unchanged.

**Therapeutics.**—Clinical experience shows that strychnine is a powerful bitter, tonic, and stomachic, stimulating digestion and increasing the appetite, a conclusion which has been elaborately confirmed by S. F. Hamper, who, using Ewald's test-breakfast, found that the drug increases the volume and digestive power of the gastric juice as well as the movements of the stomach. Strychnine is, however, more than a mere stomachic: it is a most useful tonic when there are general relaxation and loss of nerve-power. A portion of its value probably arises from its action upon the spinal motor

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\* Denied, however, by M. C. Delezenne, who states that in curarized animals the exhibition of strychnine is always followed by an abatement of the central temperature, which is often but not always accompanied by an increase in the temperature of the surface, which increase he explains by the supposition that the drug has the power of dilating the peripheral vessels.

nerve-centres; but in all likelihood it influences other portions of the cord, affecting the vaso-motor centres, and most probably also the trophic centres. Be these things as they may, strychnine is the best of all tonics in general *functional atony and relaxation*.

Many years ago Trousseau taught that in certain cases of *chorea minor* the strychnine preparations are very valuable, and Morris Benedict asserts that the remedy is useful against choreic movements. It is not probable that in such cases strychnine exerts any specific influence. H. C. Wood has experimentally proved that in choreic dogs it greatly increases the activity of the movements; and any good which it may achieve in *chorea minor* is probably due to its tonic powers.

The great influence of strychnine upon the function of voluntary motion early led to its use in cases of *paralysis*, often with the result of doing harm rather than good. It is very evident that it can be useful only when the paralysis is dependent upon, or at least accompanied by, a *depressed state* of the *spinal motor centres*. Whenever there is inflammation or irritation of these latter, strychnine may do great injury by increasing such irritation, and must never be employed. Like galvanism, in *hemiplegia* it can do only a very limited amount of good, and should not be exhibited until irritation from the clot has ceased. It is probably useful in many forms of *lead paralysis*, but when the symptoms resemble those of poliomyelitis—*i.e.*, when there is a multiple paralysis with rapid wasting of the affected muscles and alterations of the electro-contractility—we have found strychnine pushed to the verge of poisoning extraordinarily efficacious.

The value of strychnine in *amaurosis* was first asserted by Nagel. In atrophy of the essential nerve-structure experience has shown, however, that little is to be expected from it or any other remedy. To be of use the drug must, therefore, be used before the stage of atrophy has been reached. It is most useful when employed in cases of subsiding neuritis, when atrophy is imminent, as indicated by the increasing impairment of vision and the contraction of the fields for form and color. Its value in the toxic *amblyopias* is undisputed, especially where the toxic agent is tobacco or alcohol. The distressing *headache* so frequently present during the progressing atrophy of the optic nerves is often signally relieved by steadily increasing doses of strychnine or *nux vomica*, even although the advancing loss of vision is not arrested. The prompt action of the drug, secured by daily or twice-daily hypodermic injections in the temple, seems to offer better results than other methods of administration. The physiologic impression should be maintained by steadily ascending doses. Commencing with one-thirtieth of a grain, the dose can, within a few weeks, be increased to one-tenth or more, the dosage being controlled only by the tolerance of the patient, which varies greatly, a slight dryness or sense of constriction in the throat or twitching of the calves following the injection being the indications as to dosage. The acuity of vision and a widening of the fields may

often be noted within an hour after the injection, which, however, subside to former conditions as the influence of the drug disappears. It must be said, however, that in most cases of serious optic neuritis the stage of atrophy is reached and progresses in spite of all known medical measures, but in some cases strychnine seems to maintain the nutrition of the parts involved until the stage of shrinking is at an end, and thus aids in preserving permanently some increment of vision.

Strychnine in ascending doses is often of signal benefit in restoring the proper binocular balance in cases of insufficiency of the ocular muscles in debilitated patients,—*e.g.*, after attacks of influenza. The strychnine should be given hypodermically in full and ascending doses sufficient to produce and maintain a distinct physiological effect.

As a respiratory stimulant strychnine is one of our most serviceable remedies in poisoning by respiratory depressants, in *pneumonia*, in *suffocative bronchitis*, or whenever the respiratory function is failing. In long-standing *bronchitis* or *winter cough*, and in other obstinate pulmonic diseases with dilated right heart, the combination of strychnine and digitalis yields most excellent results. Much advantage may often be derived, especially in feeble subjects, by adding strychnine to the cough mixture.

The value of strychnine in the treatment of the respiratory accidents of anesthesia, which was first pointed out in the address of H. C. Wood before the Berlin Congress in 1890, is now universally acknowledged. Very frequently the best results are obtainable by using it in combination with other respiratory stimulants.

In *dyspepsia* or *constipation* or *diarrhœa*, connected with atony of the visceral muscular coat, strychnine is a very valuable remedy. In various local paralyses, such as *prolapse of the rectum*, *atonic retention of urine*, *atonic incontinence*, and *loss of voluntary motion* in certain groups of muscles from pressure upon or temporary injury of the supplying nerve, it may be very useful. There is reason to believe that it sometimes does good in these cases by influencing the nutrition of the affected muscle or the peripheral nerves; it should be injected into the affected part.

Strychnine is also a serviceable remedy as a stimulant in cases of mental and physical depression due to prolonged excitement and overwork. J. H. Musser asserts that during the strain of student-life before examinations it is especially valuable in preventing the development of *asthenopia*.

Strychnine is an extremely serviceable remedy in the treatment of *cardiac diseases* with weakness of muscle. In mitral insufficiency we have seen it prolong life for years after the failure of digitalis, and when before its administration immediate death seemed inevitable. It should always be tried in cases of failing heart where digitalis disagrees, it not being possible at present to pick out those cases in which brilliant results are to be achieved by it. To be effective it must be given in rapidly ascending doses, the patient being kept, if necessary, for weeks and months on the verge of strychnine-poison-



ing, with distinctly heightened reflexes and some muscular stiffness. Clinical experience shows that it has no cumulative action, but that the patient becomes accustomed to its use, so that a grain a day may finally be given without any serious effects. In acute *narcotic poisoning*, in serious *respiratory diseases*, in chronic *alcoholism*, and in *plumbic poliomyelitis*, whenever strychnine is used for a very decided immediate effect much larger doses should be employed than have been heretofore used. These doses should be given hypodermically at intervals of from four to six hours, under the immediate care of a trained nurse or other equally skilful person, who should vary the dose according to the effect produced. In chronic *neurasthenia* excellent results are sometimes obtained by slowly ascending doses carried over a period of one or two years.

**Administration.**—As a tonic, strychnine sulphate may be given in granule. Whenever it is desired to push the remedy to its physiological limit, it should be given hypodermically in ascending doses until restlessness, general excitement, muscular twitching, stiffness of the neck or legs, or other symptoms are manifested. In many cases of palsies, especially with trophic changes in the muscles, the best effect seems to be obtained by injecting the strychnine salt directly into the affected muscle. If proper antiseptic precaution be taken, hypodermic injections do not cause local irritation.

**Toxicology.**—Sufficient has already been said in regard to the general symptoms of strychnine-poisoning. It only remains to discuss the diagnosis. The symptoms of strychnine-poisoning usually come on with great abruptness, within from fifteen to twenty minutes, rarely an hour after the ingestion of the drug. Sometimes the convulsions are preceded by partial spasms of the muscles of the extremities, but more often the patient is suddenly thrown down by a general tetanic spasm. In this the body is bent backward and rests upon the heels and the head, in a condition of opisthotonos; the legs are rigidly extended and the feet everted; the arms bent and the hands clinched; the eyes staring, wide open; the corners of the mouth often drawn up so as to produce the *risus sardonicus*. The senses may be sharpened, but ringing in the ears and dimness of vision may be induced if the fits are severe. The face is at first pale, but, if the fit be sufficiently severe and protracted, it becomes livid from the interference with respiration. Consciousness is not affected, unless when asphyxia becomes so pronounced as to threaten death; in such cases sometimes a period of insensibility precedes dissolution, but generally the intellect is clear to the moment of death. The muscles of the jaw are usually the last in the body to be affected, but trismus finally comes on in severe cases. The spasms are generally, but not always, very painful. There are often erections of the penis, and the feces and urine may be passed involuntarily. If the case terminates favorably, the convulsions gradually lessen in intensity, and fade away, leaving the patient exhausted, with a sore, tired feeling in the muscles. After death, post-mortem rigidity is developed very quickly. Autop-

sies have revealed nothing but the usual congestive lesions of death from asphyxia, and, at times, indications of spinal hyperemia.\*

Honigmann reports a remarkable case, in which acute inflammation of the kidneys followed strychnine-poisoning.

The minimum fatal dose of strychnine is probably something under half a grain; the latter quantity has several times caused death, once in a man in twenty minutes; one-third of a grain given at intervals in fractional doses has produced such alarming symptoms as to indicate that in a single dose it might readily destroy life; one-hundredth of a grain is said to have killed a child three and a half months old; but ten grains (Tschepeke), twenty grains (A. E. Connor), also twenty-two grains (George Gray)—taken on a full stomach and retained two hours—have failed to cause death, in each case probably on account of slow absorption.†

The question as to the possibility of acquiring immunity to strychnine has become an important one in certain cases of alleged murder, and also has some bearing upon the practical use of the drug. Clinical experience undoubtedly favors the view that strychnine may be given continuously for months or years without any distinct immunity, and H. A. Hare has been unable to produce in rabbits by ascending doses any distinct lessening of susceptibility to the poison.

Death from strychnine in man and other mammals mostly occurs in a convulsion, and under these circumstances is undoubtedly due to asphyxia, caused by the unyielding, spasmodically contracted muscles. In man, death sometimes occurs not in a paroxysm, but during relaxation, and probably then is the result not only of the exhaustion following effort, but also of the direct action of the poison upon the respiratory centre and nerves.

The *diagnosis* of strychnine-poisoning should usually be comparatively easy. The rigidity during the convulsion and the exaggerated reflexes between the convulsions separate it from nearly all forms of cerebral spasms. The only conditions with which it is likely to be confused are tetanus and certain forms of hysterical convulsions. The latter may be distinguished usually by the irregular character of the spasm and the presence of hysterical stigmata. From tetanus, strychnine-poisoning can be usually easily diagnosed by the sudden onset of the poisoning, by the late involvement of the jaw muscles and the absence of rigidity between the convulsions, as well as by the more rapid course.

Cases of strychnine-poisoning have, however, occurred in which the symptoms have appeared to point towards some cerebral disease or cerebral poisoning. Thus, in the case reported by Henry Pilkington, the patient was found unconscious, surrounded by vomited matters, with excessively uneven pupils and an elevated temperature. After death both lateral ventricles were found to contain clots, and there can be little doubt that the high arterial pressure during an early convulsion had produced an apoplexy which was the cause of the subsequent symptoms and death.

\* A lesion found in one case by Moriz Rosenthal may possibly be characteristic. It consists of numerous small cross-vents in the heart-muscle, accompanied by small extravasations (*Nervenkrankheiten*, 1870, 334).

† For small fatal doses see *P. J.* and *Tr.*, viii. 1010, and *Guy H. R.*, 1865, xi. 208.

It has been asserted that in fatal cases the duration of the attack will always distinguish between natural tetanus and that produced by poison. Louis Starr, however, reports traumatic tetanus fatal in twelve hours after the first muscular twitchings, and within one hour and a half after the first convulsion; and death from tetanus has occurred fifteen minutes after the reception of the injury (Jaccoud).

In the *treatment* of strychnine-poisoning no attempt should be made to empty the stomach unless the convulsions are under control. The passage of the stomach tube may provide sufficient irritation to start a fatal convulsion, and it is probable that the irritant action of the emetics upon the mucous membrane of the stomach is likely also to prove harmful. As a chemical antidote probably the most useful substances are either compound solution of iodine or potassium permanganate. In the absence of these tannic acid may be administered. For the immediate relief of the spasms some rapidly acting depressant is required, such as amyl nitrite or chloroform. If the patient is breathing one or the other of these remedies should be given by inhalation; when the spasm is so violent as to entirely check the respiratory movements, amyl nitrite may be given hypodermically. After these substances have been administered, the most useful drugs are hydrated chloral and potassium bromide; one-half ounce of the bromide with one-half to one drachm of hydrated chloral may be given at once, and if necessary one-fourth of these quantities repeated every twenty minutes. It is essential to remember that any disturbance of the patient may, when the symptoms are well developed, bring about a fatal convulsion; thus, we have seen death occur in a convulsion caused by the effort to get the mouth open to give the remedy. If the patient is unable to swallow, the chloral or bromide may be given by rectal injection. Artificial respiration, which has been highly commended by some, cannot, we believe, ever be of service in human poisoning.

Leube was, we believe, the first to demonstrate that forced artificial respiration in animals will not only very greatly lessen the production of convulsions by strychnine, but will also affect the final result of the poisoning. After considerable discussion, the accuracy of the results reached by Leube has been finally established. The method in which the forced respiration acts is at present unknown. It has been shown by W. J. Gies and S. J. Meltzer that while artificial respiration completely suppresses the reflex irritability due to strychnine-poisoning, it does not distinctly affect the increased reflex irritability induced by section of the spinal cord: that the influence of the artificial respiration is not the result of any super-oxidation of the blood seems to be proven by the fact discovered by Gies and Meltzer, that insufflation of the lungs of the animal with pure hydrogen gas has the same effect as artificial respiration. None of the ordinary methods of artificial respiration in man is sufficiently powerful to be of any value, while the manipulations of the physician would certainly tend to increase the strychnic spasm. The curious discovery of Leube is therefore of scientific rather than of practical value.\*

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\* Gies and Meltzer found that the animal under strychnine could be kept alive by insufflation of pure hydrogen for thirty minutes, without manifesting any signs of asphyxia, dyspnoea, or cyanosis. This is so absolutely destructive of the foundations of modern physiology that it is impossible to avoid believing there was some mistake or fallacy in the experimental technic. The literature of this subject is so thoroughly given in the paper of Gies and Meltzer that we content ourselves with adding Jochelson's (*Rosbach's Untersuchungen*, i. 92).



**BRUCINE.**—Strychnine clings so closely to brucine that the physiological actions attributed to brucine may be in truth caused by contaminating strychnine. L. Wintzenreid found that brucine acts as a stimulant to the spinal cord and a paralyzant to the motor nerves, but does not influence the cerebrum or the sensory nerves; and that in the higher animals, at first it increases the arterial pressure and afterwards lessens it, in large doses paralyzes the vagi, causes death by asphyxia, and in other ways acts like strychnine. The more recent experiments of Lauder Brunton are in accord with the results obtained by Wintzenreid in showing that brucine causes spinal convulsions in mammals when injected directly into the circulation. Brunton found, however, that when taken by the mouth it produces no symptoms, probably because it is excreted as rapidly as it is absorbed. In an elaborate study, Edward T. Reichert reached the conclusion that the physiological action of brucine is precisely that of strychnine, except that brucine is much less rapidly absorbed, is from forty to fifty times less powerful as a convulsant, is more poisonous to the sensory nerves, and is more uncertain in its effect upon bodily temperature. Further, brucine appears to have an action upon the volitional centres of the frog different from that of strychnine, producing a brief period of motor paralysis preceding the stage of spinal convulsion (Mays, Reichert).<sup>\*</sup> Thomas I. Mays found that brucine locally applied to the nerves of the frog rapidly produces a paralysis of the sensory fibres. This led him to test it as a local anesthetic in man, and he asserts that a five- or ten-per-cent. solution applied to the mucous membrane of the mouth caused rapid loss of sensibility; also that a twenty-per-cent. solution applied to the back of the hand caused pronounced impairment of sensibility. Mays used this solution with excellent results for the relief of the itching of chronic *pruritus*. Ralph W. Seiss and Charles H. Burnett have found that the application of a five-per-cent. solution in the local *pruritus* of inflammation in or about the external ear usually gives very marked relief. Burnett states that his results were far more satisfactory than those which he has obtained with cocaine. In using brucine as a local anesthetic it is essential that it be chemically pure: the *nitrate* or the *sulphate* may be selected, and one minim of hydrochloric or sulphuric acid should be added to the solution for each three grains of the alkaloid salt.

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<sup>\*</sup> For a research showing the comparative action of strychnine and brucine on different species of frogs, see Sautesson (*Archiv f. Exper. Path. u. Pharm.*, XXXV.).



## FAMILY VI.—DEPRESSO-MOTORS.

UNDER this heading are considered certain drugs which are used for the purpose of lessening the activity of the spinal cord. They have, except in this particular, but little in common in their action, and must be studied individually.

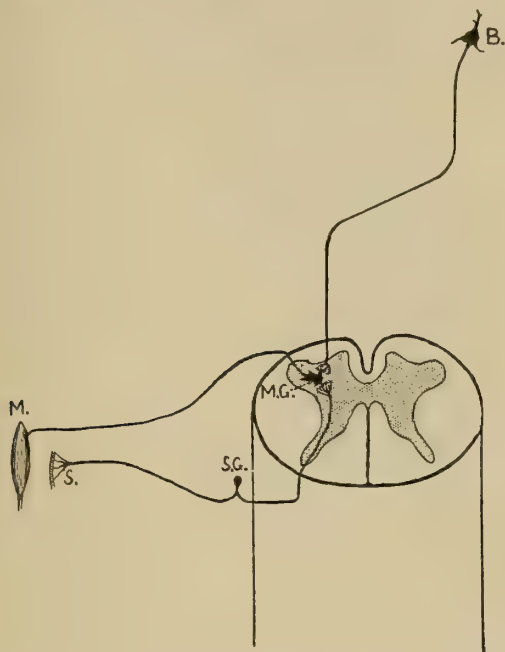


FIG. 10.—DIAGRAM TO ILLUSTRATE THE ACTION OF THE DEPRESSO-MOTORS.

B.—Psycho-motor centre in the brain. M.G.—Motor ganglion in spinal cord. M.—Muscle. S.—Sensory nerve endings. S.G.—Ganglion on the posterior (sensory) nerve root.

Paralysis of the motor ganglia or motor nerve abolishes both voluntary and reflex movement; paralysis of the sensory system destroys reflex but not voluntary motion because the pathway from the brain to the muscle remains intact.

Physostigmine, the Nitrites, Gelseminine and Chloral Hydrate depress M.G. The Bromides depress S.G. Lobelia, Coniine, and Gelsemine paralyze the motor nerve endings in M. Ether and Chloroform depress both M.G. and S.G.

### PHYSOSTIGMA.

This substance commonly known as Calabar bean is an irregular, kidney-shaped bean, about an inch in length and three-fourths of an inch wide, the product of the *Physostigma venenosum*, a perennial woody creeper of Calabar, Africa, where the bean has been used by the natives as an ordeal test for criminals, witches, etc., since time immemorial. It owes its activity to the alkaloid *physostigmine*, or *eserine*, of which it should contain 0.15 per cent. E. Harnack and L.



Witkowski have described a powerful tetanizing alkaloid, *calabarine*, which is sometimes abundant in commercial extracts of Calabar bean. It is probably a decomposition product from that alkaloid (see also Husemann). *Isophysostigmine* according to Ogiu is similar in its action to physostigmine but more powerful.

### Official Preparations:

Extractum Physostigmatis.....	$\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.015 Gm.).
Tinctura Physostigmatis (10 per cent.) ..	20 to 40 minims (1.2–2.5 C.c.).
Physostigminæ Salicylas [Eserine Salicy-	
late].....	$\frac{1}{60}$ to $\frac{1}{30}$ grain (1–2 Milligm.).
Physostigminæ Sulphas.....	$\frac{1}{60}$ to $\frac{1}{30}$ grain (1–2 Milligm.).

*Absorption and Elimination.*—No apparent irritant action occurs from therapeutic doses of Calabar bean or its alkaloid.

Both absorption and elimination are very rapid. N. Teich and D. Schweder have both found physostigmine in the urine half an hour after its ingestion. Although the alkaloid has been detected in various secretions by Dragendorff and his pupil Pauder, it chiefly escapes through the kidneys. Its effect upon the urinary secretion has never been studied, excepting in that Merson states that it decreases the excretion of urea and other urinary solids in paresis.

**Physiological Action.**—*Nervous System.*—Physostigmine is a depressant to the motor side of the spinal cord. Upon the cerebrum it has no perceptible influence. It is feebly depressant to both motor and sensory nerves but the paralysis and loss of reflex activity which it produces are undoubtedly due to its action upon the cord.

When an animal receives a small fatal dose of Calabar bean, after a time muscular tremors appear, and almost immediately the victim falls to the ground, or lies down, in a state of perfect muscular flaccidity. The pupils generally contract, and the respirations become slow, irregular, and often stertorous. All reflex actions are almost at once diminished, and this diminution grows greater and greater, until it ends in their complete abolition. So long as the condition of the motor system allows of it, evidences of sensibility are manifested whenever the animal is in any way injured. According to Clementi Papi, the voice is completely lost. The muscular tremors persist during the whole period of paralysis, and, indeed, even after cessation of the respiration. They vary greatly in intensity, and in some cases are so severe (Fraser) as to simulate general convulsions. As the minutes go by, the rhythm of the respiration becomes more and more affected, and at last death takes place from asphyxia.

Fraser, Harnack, Witkowski, and others have found that if in the frog a peripheral nerve be protected by tying its artery and the batrachian be poisoned with Calabar bean, the paralysis in the protected limb occurs *pari passu* with that in the remainder of the body. Further, Fraser has found that when the poison is applied directly to the cord, fibrillary contractions, due probably to a local irritant influence, are induced in the muscles supplied from below the point of application, but in a little while all movements cease, and even galvanization of the cord itself is unable to elicit response. It is asserted by Papi and other investigators that the extremely minute dose of physostigmine acts as a stimulant to the spinal cord. Although this may be true, it seems at present writing improbable.\*

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\* Köhler, Rossbach, and others have affirmed that Calabar bean produces a tetanic intoxication. A plausible explanation of these singular observations, and of many of the discrepancies of authorities, is to be found in the discovery of calabarine. Its discoverers state that it produces first a violent tetanus, and afterwards paralysis. It is plain how its presence in varying amounts in Calabar

Although there is reason for believing that physostigmine is capable of affecting both motor and sensory nerve-trunks, yet this action is so feeble as probably to take no part in the production of symptoms. The afferent nerves are less sensitive than the efferent, since Fraser has found, first, that the local application of a strong solution of the poison to a nerve kills the efferent or motor fibres before the afferent or sensory, although the functions of both of them are finally abolished; second, that when the arteries in the left leg of a frog are tied, and the animal poisoned both with Calabar bean and strychnine, there comes a time when reflex movements are excited in the left leg by irritation of the right foot, although irritation of the left foot does not cause movements in the right leg,—i.e., the impulse is able to travel up the poisoned nerve of the right leg but not down it.

The extreme feebleness of the influence of physostigmine is shown by the fact that the frog's nerves are often active after death from physostigma (Laschkewich, Vintschgau, and Fraser); and Fraser has determined that after the fatal result has been produced rapidly with physostigmine, the rate of conduction of impulse is as rapid in the nerve to which the poison has had free access as in one which has been protected by the tying of its artery.

Loss of power in the motor nerves after poisoning by Calabar bean has been found only in the frog, and further, only when the dose has been so small that the heart has continued to beat long after the cessation of respiration, so that the nerves had been, as it were, macerated in a solution of the poison. Harnack and Witkowski deny that physostigmine has even this feeble influence upon the nerve-trunks. The loss of power is probably in the termination of the nerve rather than in the trunk, for Fraser found that when all the blood-vessels supplying the gastrocnemius muscle were cut in a frog and the animal poisoned, at a certain time irritation of the crural nerve produced spasms of the gastrocnemius alone.

*Muscles.*—The large dose of physostigmine produces violent muscular tremors. The continuance of these movements after death indicates that they are due to a direct action of the drug upon the muscles. This conclusion is established by the experiments of Laschkewich, of Fraser, and of Leven and Laborde. All of these investigators have noted that after death these contractions are increased by exposure to the air and by direct stimulation of the muscles; and Fraser has found that they occur in the frog during life after section of the supplying nerve, and also in a muscle actually cut out of the body. Laschkewich has confirmed the latter fact in the case of warm-blooded animals, and Leven and Laborde have proved that previous destruction of the lower end of the spinal cord in a guinea-pig does not prevent the development of the muscular twitchings in the hind legs. Schweder contends that the action of the poison is not, however, upon the muscular structure itself, but upon the peripheral nerve-endings in the muscle, basing his conclusions especially upon the asserted fact, that previous hypodermic injections of atropine or curare prevent the development of rigidity in the snake poisoned with physostigmine. It is certain that the final paralysis produced by physostigma is not of muscular origin, since at the time of death the contractility of the muscles is in no way diminished, but, on the contrary, Fraser has noted that loss of contractility and rigor mortis are greatly delayed in Calabar-bean poisoning.

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bean preparations would modify their action. The researches of Köhler, of Vintschgau, and of Rossbach and Fröhlich are especially open to doubt, on account of their statements that Calabar bean tetanizes. It is very probable that the extracts used by them contained a notable percentage of calabarine.

*Circulation.*—In the mammal, after therapeutic and even toxic doses, the cardiac action of physostigmine is subordinate to its influence upon the nerve-centres. In moderate doses, however, it causes a marked slowing of the pulse with some rise in the arterial pressure. The slowing of the pulse is probably due to a stimulation of the intracardiac terminals of the vagi, although some authorities attribute it to an action on the heart-muscle. The rise of pressure is brought about by an influence on either the heart or arterial muscles. As has been shown by Fraser, when overwhelming doses of the poison are administered, especially if they be injected into the jugular vein, death results from syncope, or from consentaneous failure of the cardiac and the respiratory functions, and the heart is found arrested in diastole, flaccid, but, according to Fraser and to Arnstein and Sustschinsky, responding, though feebly and uncertainly, to direct stimulation. In the poisoned frog the early contractions of the heart are slower and more forcible than the normal (Harnack and Witkowski); while the arrested heart is insensible to stimuli (Rossbach and Fröhlich).

Although, according to the experiments of Fraser, there is at first a slight fall of the blood-pressure, which is probably due, as he believes, to diminished pulse-frequency, yet, in spite of the continuance of the slow pulse, the arterial tension soon recovers itself, and remains for a long time much above the normal point, while at the same time the individual cardiac beats are greatly increased in strength (Fraser, Bezold and Götz\*). Finally, the arterial pressure falls far below normal, and the power of the heart is gradually extinguished.

That the rise of arterial pressure must be largely the result of a stimulant action upon the heart or upon the vessel-walls is shown by the finding of Bezold and Götz, that the arterial pressure still rises under the influence of physostigmine after section of the spinal cord; and by that of Harnack and Witkowski, that when the vaso-motor centres are paralyzed with chloral, physostigmine causes a very decided increase of the arterial pressure. The facts—that section of the vagi does not interfere with the production of the cardiac phenomena of Calabar bean, and that in the frog physostigmine acts in its usual way on the heart, although the brain and medulla have been destroyed (Vintschgau); also that when physostigmine is placed directly on the heart, or into one of its chambers, it causes a long diastolic pause, followed by contractions, interrupted by pauses, and finally by resumption of regular contractions, or else by diastolic arrest, the heart still retaining its power of responding in an embarrassed manner to stimuli (Fraser)—would appear to demonstrate that physostigmine directly affects the heart. How far this influence is upon the cardiac ganglia and how far upon the muscle-fibre has not been determined. It seems, however, probable that physostigmine affects the cardiac muscles in the same way as it does the muscles of voluntary life.

There is, however, much reason for believing that physostigmine affects the peripheral inhibitory apparatus, although the evidence is not entirely clear. Arnstein and Sustschinsky found in rabbits and also in guinea-pigs that the influence of galvanic irritation of the vagi upon the heart is much greater after than before poisoning with physostigmine, diastolic arrest being produced much more easily and continuing much longer than normal after the withdrawal of the stimuli. Moreover, after having completely paralyzed the peripheral cardiac vagi in the rabbit by large doses of atropine, they restored functional power to these nerves by injections of Calabar bean. If the accuracy of these experiments be admitted, it must

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\* We have not seen the original paper of these authorities in the *Centralblatt für Med. Wissenschaft*, 1867, but quote them from the paper of Arnstein and Sustschinsky.



also be admitted that physostigmine is a powerful stimulant to the peripheral cardiac inhibitory apparatus. Köhler, however, using the frog, and Rossbach and Fröhlich, using the rabbit, failed to resuscitate the atropinized vagi by means of physostigma, but a negative result in such a case might be due to an improper proportion in the doses of the counter-poison, or to the atropine being employed in overwhelming amount.

Physostigmine appears to have no paralyzing effect upon the vagi; at least in warm-blooded animals these nerves are never paralyzed (Fraser, Arnstein and Sustschinsky, Harnack and Witkowski); and the loss of functional power which has been detected by Fraser, Rossbach and Fröhlich, Harnack and Witkowski, in the vagi of the frog does not appear until so long after the cessation of respiration that it is very probably a secondary result.

The question as to the effect of physostigmine upon the blood-vessels cannot at present be positively answered. Evidence concerning it has been brought forward by Fraser and Harley in the form of observations made upon the web of the frog. We have already stated our belief that this sort of evidence is of very little value. In the present instance, as usual, it is entirely contradictory as given by different observers. (For details, see tenth edition of this treatise.)

The fact that the rise of arterial pressure produced by physostigmine after section of the cord is not nearly so great as in an uninjured animal suggests, but does not prove, that the drug affects the vaso-motor centre. Analogy makes it probable that the muscular fibres in the coats of the vessels share the wide-spread muscular action of the poison, and that the peripheral contraction of the arteries is an efficient cause in producing rise of blood-pressure. In considering the general physiological action of the drug, it must not be forgotten that its influence upon the heart is entirely subservient to its influence on the nervous system,\* and that death in the mammal occurs before the stage of cardiac palsy is reached unless the drug be injected directly into the heart in overwhelming dose.

*Blood.*—According to Fraser, after death from physostigmine the blood coagulates slowly and loosely, and the red disks present various irregularities of outline; it is probable that these changes are due to the long asphyxia, and that the poison does not directly affect the blood.

*Intestines.*—Intestinal peristalsis is primarily much increased by the action of physostigma (Westermann, Papi, Fraser). After poisonous doses there is at first a stage of exceedingly active movements in the bowels; then spasmodic tetanic contraction of the intestines occurs, so that their calibre is very much diminished; and finally relaxation and dilatation take place. After death the vermicular movements are found very much lessened (Fraser) or altogether abolished (Tachau). The action of the drug upon the intestines appears to be peripheral, due to contact of the poison in the blood with the muscular fibres or the nerve-elements in the walls of the bowels; for Westermann found that extirpation of the cardiac ganglion had no effect upon the action of the drug, but that tying of the mesenteric and of the cœliac arteries, before poisoning, prevented any increase in the peristalsis.

*Secretion.*—Physostigmine probably increases nearly all secretions. Its action upon the salivary glands is often decided, and, according to Heidenhain, is not prevented by atropine.

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\* For a discussion of the peculiar cardiac relations of physostigmine and muscarine, see the paper by Harnack and Witkowski. Those authors believe that Calabar bean sets in motion the heart arrested in diastole, not by paralyzing the cardiac inhibitory apparatus, but by stimulating the cardiac muscle.

*Eye*.—Physostigmine produces a contraction of the pupil, when applied locally, by its effects probably upon the peripheral endings of the nerves. In its action there is probably a combined paralysis of the peripheral terminals of the sympathetic and stimulation of the oculo-motor nerve-endings. Within certain limits it will overcome the effect of atropine.

The closeness of the analogy between the pupillary action of atropine and that of physostigmine is seen in the fact that, like the former, the latter, as shown by the experiments of Vée and Leven on chickens, does not affect the irides of birds. It is probable that the two alkaloids are directly antagonistic in their action upon the peripheral nerve-endings in the pupil.

It has been held by various authorities that if galvanization of the sympathetic fibres in the neck fails to expand a contracted pupil, the myosis must be due to paralysis of the sympathetic. Evidently, however, this is asserting too much, for, as pointed out by Grünhagen, it is conceivable that an oculo-motor spasm can exist of such intensity that the antagonistic nerve is unable to dilate the pupil. The testimony as to whether galvanic stimulation of the sympathetic does or does not dilate the physostigminized pupil is somewhat conflicting. Schultz, and Grünhagen, each affirms that dilatation always occurs; while, on the other hand, Gustav Engelhardt has found that galvanization of the cervical sympathetic has no effect upon the physostigminized pupil. The experiments of Fraser, of Bernstein and Dogiel, and of Rosenthal would seem to reconcile these differences, and, by their accord, to prove that under the maximum influence of Calabar bean the sympathetic nerve is powerless, while when the contraction is the result of a milder influence of the drug, stimulation of the sympathetic nerve will cause some dilatation.\* Fraser, and also Engelhardt, have found that if the poles of a battery be applied directly to an iris even most profoundly contracted by physostigma, immediate dilatation occurs.

On the other hand, the well-known force of the myosis indicates that it is not due simply to loss of power in the dilating fibres; an indication which is corroborated by the fact that section of the cervical sympathetics will not produce a myosis as complete as that caused by physostigmine.

**SUMMARY.**—The dominant physiological action of physostigma is a persistent depression of the motor centres of the spinal cord, involving also the respiratory centres in the medulla, and producing loss of reflex action with an increasing paralysis, ending in death from centric paralytic asphyxia. Contraction of the pupil is usually seen in the poisoning, and is always produced by the local application of the drug; it is due to a peripheral influence and probably to paralysis of the sympathetic nerve-filaments with stimulation of the oculo-motor nerve-endings. The motor nerve-trunks are scarcely affected, but in slow poisoning probably suffer some depression of function which especially affects their peripheral endings. Neither the cerebral cortex nor the sensory nerve nor the sensory nerve-centres are acted upon, unless secondarily in the latest stages of poisoning. Physostigma acts as a stimulant directly either upon the muscle structure itself or upon the peripheral nerve-endings in the muscles. The influence of the drug upon the circulation is entirely subordinate. Early in the poisoning there is a rise of the blood-pressure, which is in great part, if not alto-

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\* More recently Rossbach and Fröhlich affirmed that galvanization of the sympathetic still causes dilatation, even when the action of the physostigmine is most vigorous. As it is scarcely conceivable that the various other investigators should have been so much in error, it is probable that Rossbach and Fröhlich used such strong currents that they were directly transmitted to the iris.

gether, due to a direct stimulation of the cardiac muscle or its contained ganglia, although it is probable (not proved) that there is some contraction of the blood-vessels, which may be due to an influence upon the muscle-fibre in the vessel-walls similar to that upon other muscle-fibres, striated and non-striated. We have no information as to the effect of the poison on the vaso-motor centre. According to some authorities, the peripheral vagi are strongly stimulated. Intestinal peristalsis is greatly increased by the direct action of physostigma upon the muscular fibres or the peripheral nerve-endings in the intestinal walls. The alkaloids of Calabar bean are rapidly absorbed, and are eliminated chiefly by the kidneys.

**Therapeutics.**—The action of physostigma upon the spinal cord very early led to its use in spasmodic affections, and especially in *tetanus*. In the paper of B. Roemer are collected forty-seven cases, of which twenty proved fatal.\* In *trismus neonatorum*, it has been employed with results certainly no more encouraging than those obtained in tetanus. In *chorea* it has also been used by some practitioners with asserted advantage, but further experience hardly justifies its administration.

The physiological action of physostigmine upon the unstriated intestinal muscle-fibres has led to its employment in *atony* of the muscular coat of the bowels and other similar organs. V. Subbotin has used the extract with the happiest results in a case of *chronic bronchial catarrh* with intense *dyspnœa*, believed to be due to weakness of the bronchial muscular fibres, and also in one of apparently "*phantom tumor*," with *chronic intestinal dyspepsia* and *catarrh*. In *constipation* dependent upon relaxation, and as an addition to laxative pills, we have found it very useful. A. Hiller strongly endorses the value of the extract in *chronic intestinal atony*, after or during a *catarrh*, in the convalescence from fever, etc., and in *constipation* with flatulence, in *meteorism*, etc.

Calabar bean has also been employed in *strychnine-poisoning*, and a recovery obtained after the ingestion of three grains of the latter alkaloid is reported by J. W. Keyworth.

In *epilepsy*, some trials have been made of the drug, but its value is very doubtful. Harnack and Witkowski have found that in epileptic guinea-pigs physostigmine causes a succession of fits lasting for hours and days. They have further noted a similar influence upon man. Attention has also been called to the employment of physostigma as a *galactagogue*, the extract being applied to the breast itself.

**Ophthalmic Uses.**†—The instillation of a drop of a one-quarter to one-half-per-cent. solution of eserine sulphate into the eye is followed by strong contraction of the sphincter of the iris and by spasm of the ciliary muscle which adapts the eye for the near point. Its action begins in about one minute, usually reaching its maximum in from twenty to thirty minutes, and lasts from twenty-four to thirty-six

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\* For references to additional cases see 13th edition of this work.

† This section has been written by Professor George E. de Schweinitz.



hours. The intra-ocular tension is reduced, provided it has been raised above the normal point before the application of the drug. Eserine, when first instilled into the eye, is apt to produce twitching of the eyelids and sharp supra-orbital pain due to its causing spasm of accommodation. It is used by ophthalmologists: *First*, to reduce abnormally high intra-ocular tension, particularly in *glaucoma*, and in those ocular conditions in which, other things being equal, it is desired to diminish the intra-ocular tension; *second*, to prevent *prolapse of the iris* after simple cataract extraction, and sometimes to reduce a prolapse when this has occurred in the periphery of the cornea as the result of an operation or of a perforating corneal ulcer; *third*, to limit the progress of deep *ulcers* near the margin of the cornea, because it is supposed to promote absorption through dilatation of the ciliary vessels and to check the sloughing process; *fourth*, to counteract the effect of the milder acting mydriatics,—for example, homatropine,—especially in eyes in which their use has tended to raise intra-ocular tension; *fifth*, to overcome paresis of the ciliary muscle resulting from various diseases,—for example, diphtheria, diabetes, syphilis; *sixth*, to reduce the vascularization in certain types of *keratitis*, *episcleritis*, and *scleritis*, provided there be no associated iritis. Eserine too freely used, especially in hyperemic eyes, is capable of causing slight iritis, the so-called eserine iritis. If the indications for a local anesthetic are present in conjunction with those demanding a myotic, there is no objection to combining in the same solution eserine and cocaine, or eserine and dionine.

**Administration.**—Physostigma is frequently administered as an extract, but the alkaloid is preferable, on account of its certainty. The salicylate is preferable to the sulphate as more permanent, the sulphate being very deliquescent.

**Toxicology.**—So far as we know, Calabar bean has not been used, either in Europe or in this country, with criminal intent. In Liverpool seventy children were accidentally poisoned at one time.\* Many of the victims vomited spontaneously, and thus relieved themselves. Those brought to the hospital were in a state of extreme prostration and muscular relaxation. They appeared to suffer almost no pain, some of them, however, saying that they had a “belly-ache.” Among some thirteen examined, one had the pupils contracted. The only child who did not recover was excessively weak, and, crying out suddenly, was dead of syncope. The heart was found relaxed and flabby, both sides equally full of blood. Half a bean produced in a strong man† great muscular weakness, tightness across the chest, temperature of 96.6° F., very slow, intermittent, irregular pulse, and collapse, without vomiting, purging, contraction of the pupils, or abdominal pain. Lodderstaedt reports a hypodermic injection of one-half a milligramme of the physostigmine sulphate in a boy nine years old, followed in a quarter of an hour by violent headache, free sweat-

\* See *M. T. G.*, Oct. 1864, 406.

† See *St. Bartholomew Hosp. Rep.*, 1879, xv.

ing, salivation, slowing of the pulse, repeated vomiting, contraction of the pupils, and, finally, deep collapse, from which, however, the patient recovered. Two girls took between them 0.1 gramme (1.53 grains) of physostigmine, with the result of sudden unconsciousness, great redness of the face, muscular relaxation, vomiting, widely dilated, immovable pupils, and, on recovery of consciousness, violent abdominal pains, with pulse 60, and hard; recovery after some hours (Leibholz).

In 1864 Kleinwachter first used successfully atropine in physostigma-poisoning, and thereby started much discussion and research.

Bourneville detailed in 1867 some experiments which seemed to show that there is a real antagonism between Calabar bean and the mydriatic, and in 1870 published five experiments upon guinea-pigs, which were very decisive in that a proved fatal dose of physostigmine was given in each case and recovery obtained by the use of non-lethal doses of atropine. In 1869 Roberts Bartholow, of Cincinnati, on the strength of a few really indecisive experiments, arrived at a conclusion opposite to that of Bourneville.

In an extremely thorough research, which might well serve as a model to any one studying the antagonistic action of poisons, Fraser demonstrated that within certain limits atropine may be relied upon as a counter-irritant poison to physostigmine. He found that in the rabbit one-fiftieth of a grain of atropine could successfully antagonize one and a half but not twice the minimum fatal dose of Calabar bean, one-fortieth of a grain of atropine could overcome two to two and a half times the minimum lethal dose of physostigmine, and three-fiftieths was sufficient for three times the minimum fatal dose. When four times the lethal dose of physostigmine was given to the rabbit, atropine was powerless to do good. In all these cases the atropine was given five minutes after the physostigmine. No experiments were made by Fraser to test the value of physostigmine in atropine-poisoning. These experiments of Fraser have been in some degree confirmed by the imperfect researches of Amagat.

J. Pal asserts that physostigmine is an antidote to curare; it being possible with it to bring about voluntary respiration in an animal which has been entirely paralyzed by the South American poison. We know of no experiments as to the value of curare in physostigmine-poisoning.

### HYDROBROMIC ACID.

Hydrobromic acid is recognized by the Pharmacopœia in the form of a ten-per-cent. solution. This is a colorless, odorless liquid with a strongly acid taste. On account of its irritant action upon the stomach it is comparatively little used in the form of the acid itself but is chiefly employed in the form of one of its salts. Of these there are official, ammonium, calcium, lithium, potassium, sodium and strontium bromides.\* These all occur in the form of colorless or white crystals of a bitterish salty taste, freely soluble in water and, with the exception of potassium bromide, also soluble in alcohol. All except the potassium and ammonium salts are more or less hygroscopic.

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\* Zinc bromide is also official but has no useful place in therapeutics.

*Incompatibilities.*—The hydrobromides of many of the alkaloids are insoluble in water and therefore care should be observed in combining bromides in solutions containing alkaloids. Potassium chlorate and tincture of ferric chloride liberate free bromine when brought into contact with the salts of hydrobromic acid. The bromides are also incompatible with spirit of nitrous ether and with calomel.

#### Official Preparations:

Acidum Hydrobromicum Dilutum (10 per cent.).....	1 fluidrachm (4 C.c.).
Ammonii Bromidum.....	10 to 60 grains (0.6–4.0 Gm.).
Calcii Bromidum.....	10 to 60 grains (0.6–4.0 Gm.).
Lithii Bromidum.....	10 to 60 grains (0.6–4.0 Gm.).
Potassii Bromidum.....	10 to 60 grains (0.6–4.0 Gm.).
Sodii Bromidum.....	10 to 60 grains (0.6–4.0 Gm.).
Strontii Bromidum.....	10 to 60 grains (0.6–4.0 Gm.).

*Absorption and Elimination.*—The bromides are freely absorbed and circulate in the blood as a bromide. Elimination takes place to a certain extent through the skin, and probably largely through the intestinal mucous membranes, though the chief avenue is the kidney.

P. Guttman has recognized bromine in the contents of the acne pustules of bromism; Bill detected the bromide in marked quantities in the feces of men taking it; and H. Quincke found that when forty grains of sodium bromide were given to dogs with intestinal fistula, two and a half hours afterwards the intestinal juices were free from the bromide, which reappeared in them three to six hours later. The salt has been found by Voisin, Amory, Namias, Bill, etc., in the saliva and in the urine, and by Amory in the perspiration. In the body of a man who died while taking it, M. Namias found it in all the liquids, as well as in the brain, liver, spinal cord, lungs, etc. The rapidity of elimination seems to vary: thus, Amory recovered one-half of the amount ingested during the first, and one-third during the second, twenty-four hours, and Ware (Thesis of H. P. Bowditch) obtained a little more than half of the amount ingested in the urine of the succeeding thirty-two hours, while Bill was not able to get more than one-eighteenth of it during the first day. Bill has frequently found the bromide in the urine two weeks after the last dose has been exhibited; and Rabuteau has seen its presence persist under similar circumstances for a month. According to T. Hondo, when the diet is rich in sodium chloride the bromides are eliminated much more freely than when common salt is withheld.

When a bromide is given continuously it accumulates in the body and may be found in every tissue, but, according to Doyon and Cazeneuve (confirmed by Féré and Herbert), it is stored up in the nerve-centres much more largely than elsewhere.

**Physiological Action.**—The bromides in sufficient concentration are poisonous apparently to all forms of animal protoplasm. They show, however, a selective action upon the nervous system.

*Nervous System.*—In man and the higher mammals the first action of the bromides is upon the brain, in which they seem to depress both the intellect and the psycho-motor areas. After larger doses there is also depression of the spinal cord. In the frog the bromides give a loss of reflex power at a time when voluntary motion persists, indicating that their first action in these animals is upon the sensory side of the spinal cord. In larger quantities there is also depression of



the motor tracts in the cord. It is probable also that in these animals there is a depression of the sensory nerve-endings. That a large dose is capable of affecting the sensory system in man, as well as in the frog, is shown by the fact that in several cases more or less complete general cutaneous anesthesia has followed the ingestion of the bromide.

Potassium bromide administered to frogs in minute doses produces as a first result a tetanoid condition, in which there may be very marked opisthotonos. After a short time this stage of muscular excitement gives way to one of great muscular relaxation and total abolition of reflex actions. Voluntary movements, however, often occur during this period, and the frog which has been lying limp and apparently dead will startle the observer by a sudden vigorous leap. This fact has been so frequently witnessed that there can be no doubt of its truth.\* Very early in the paralytic stage the respiratory movements are affected, and they gradually grow less until their final arrest. Upon mammals (Eulenberg and Guttman) the bromide acts very much as upon frogs, inducing progressive paralysis, depression of temperature, and death by asphyxia when given in small poisonous doses; and great disturbance of the circulation, with finally diastolic arrest of the heart, when very freely administered.

The persistence of voluntary movement in the frog after the abolition of reflex actions shows that the influence of the drug is not chiefly exerted upon the cerebral centres of motor impulse, nor upon those cells of the cord which originate movement, but upon either the afferent nerves or those portions of the cord which transmit the impulse from these nerves to the cells presiding immediately over motion. Both Lewisky and Purser found that death occurred from small doses before the motor nerve-trunks and the muscles had lost their irritability (confirmed by Saisson). This being so, the question arises whether the paralysis be spinal or due to paralysis of the peripheral afferent nerves. There is an apparent conflict in the evidence upon this point. Eulenberg and Guttman found that when access of the poison was prevented to one or more limbs by tying the arteries, reflex actions were abolished in these parts as rapidly as in others. Similar results have been obtained by Lewisky, by Roberts Bartholow, by Purser, and by Laborde. On the other hand, Damourette and Pelvette assert a contrary result. Unfortunately, they do not give the details of their experiments. They state, however, that if the lumbar plexus of vessels be tied before the poisoning, the fore feet lose their reflex activity before the hinder. It seems well established that cutaneous anesthesia in greater or less degree accompanies the loss of reflex activity; for, as Purser says, a poisoned animal quite able to jump submits to pinching, pricking, burning, etc., without moving. Eulenberg and Guttman have seen the same thing in some rabbits. Damourette and Pelvette have noticed a condition in which electrical stimulation of a nerve-trunk produced marked reflex action, although no excitement of the skin supplied by the afferent fibres of the nerve was capable of doing this, showing that the extremities of the sensitive nerves are affected before the trunks. The evidence is, we think, sufficient to prove that the bromides affect all parts of the nervous system of the lower animals, but that the cerebrum, the motor tract of the cord, and the efferent nerves are the last portions to be affected; that the most sensitive to its action is the receptive portion of the cord,—that which receives and transmits reflex impulses,—and next to this, and perhaps almost equally susceptible with it, are the peripheral ends of the afferent nerves.

Upon the cerebrum of the higher animals the bromides undoubtedly exert an influence, and the researches of Albertoni have thrown much light upon the usefulness of the drug in epilepsy. That observer found that when administered to dogs the bromide depresses very markedly the power of the motor zone of the cerebral cortex to respond to stimuli, and to give forth, on decided irritation, epileptic discharges; it was also discovered that this action of the bromide was much more

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\* It is vouched for by the following observers: J. M. Purser, Lewisky aus Kazan, J. V. Laborde, Damourette and Pelvette.

decided when there had been a prolonged saturation of the system with the drug than after a single large or even toxic dose. According to the researches of A. Crisafulli, the action of the bromides upon the cells of the cerebral cortex is so powerful that vacuolization and other demonstrable changes are produced by it. The intellectual symptoms of bromism show that in man the action of the bromide on the cerebral cortex is more marked than in the lower animals, on account, no doubt, of the higher cerebral development. The drug in other respects acts upon man as upon lower mammals, lowering the reflex excitability of his spinal cord, paralyzing the ends of the peripheral nerves, etc.

According to the researches of B. Schulze, there is under the influence of the bromide a decided decrease in the elimination of phosphorus,—an indication that the protoplasmic molecular changes in the nervous system are lessened by the drug.

*Circulation.*—The experiments of J. G. Schouten and others have shown that potassium bromide when given in large doses lowers the blood-pressure by weakening the heart. This effect is, however, probably to be attributed to the potassium rather than to the hydrobromic acid. In the physiological studies of E. T. Reichert, hydrobromic acid was found to produce a temporary elevation of the blood-pressure, which was attributed, without proof, to vaso-motor spasm of peripheral origin. Large doses were directly paralyzant to the heart.

*Temperature.*—In warm-blooded animals, toxic doses of potassium bromide lower very decidedly the temperature. There have been no calorimetric experiments to determine whether this fall of temperature is due to a diminished heat-production or an increase in heat-elimination.

*Nutrition.*—The symptoms of bromism show that hydrobromic acid has a distinct influence upon the general nutrition. The experiments of Schulze, Chittenden and Culbert seem to show that bromides increase the excretion of urea but diminish the output of phosphorus. Rabuteau on the other hand in a single experiment found that the elimination of urea was slightly diminished by potassium bromide.

**SUMMARY.**—When in sufficient concentration hydrobromic acid acts as a powerful depressant upon all of the higher tissues. It is absorbed rapidly and eliminated in all the secretions more slowly; so that when given continuously it accumulates and causes *bromism*. The portions of the human organism most sensitive to its influence are the whole cerebral cortex, the receptive side of the spinal cord, and the afferent peripheral nerve-endings. The influence of the bromides upon the circulation is subordinate to its action on the nervous system.

**Therapeutics.**—The bromides are employed by the therapist to quiet *cerebral excitement* when not inflammatory in its nature; to lessen over-susceptibility of the spinal centres of reflex action, or of the peripheral afferent nerves which lead to these centres; and to subdue nervous excitement of the genital system.

The bromides are contraindicated by an excessive irritability of the gastro-intestinal mucous membrane; when such condition exists they may provoke exhausting diarrhœa. Great exhaustion, and

especially great nutritive exhaustion of the nerve-centres, is a contra-indication to their use. Thus, owing to the excitement that attends *confusional insanity*,—i.e., the insanities following child-birth, typhoid fever, surgical operations, etc.,—bromides are frequently administered in large doses, to the great detriment of the patient. We are well convinced that under such circumstances they greatly lower the nutrition and check recovery. In the same way, in *cerebral softening*, *senile dementia*, and allied disorders, they must be used, if at all, only with the greatest reserve.

There are various forms of *nervous excitement*, or unrest, such as sometimes follow excessive intellectual toil, anxiety, and other nervous strain, or occur during convalescence from acute disorder, in which the salt now under consideration is very valuable. The same may be said of some forms of *hysteria*. In some cases of *neuralgia* the bromide affords great relief, but in the majority of cases it fails. It has seemed to us useless in neuralgia dependent upon anemia or want of power; and our experience agrees with that of Anstie, that it is especially useful in persons of good nervous power, muscular force, and activity of circulation. As an hypnotic, it is employed in wakefulness from nervous excitement and in *delirium tremens*, but is of very feeble power.

The chief use of hydrobromic acid is to lessen motor activity. It is especially in *epilepsy* that it has attained a well-deserved reputation, doing far more good than all other remedies combined, sometimes apparently effecting cures, more commonly ameliorating the symptoms, but occasionally failing entirely. There is no known method of distinguishing before trial with any certainty in what cases it will do good. The assertion of Trousseau, that it is least efficient in the mild form of the disorder known as *petit mal*, accords with our experience. The most brilliant results have, as a rule, been obtained in cases of not too long duration in which the fits were frequent and severe. The governing principle in its use is to try it in every case, increasing the dose until a mild degree of bromism is induced, and being guided by the results.

The drug is also often efficacious in various reflex spasmodic neuroses: in the *vomiting of pregnancy* or of *uterine diseases*; in the *gastric convulsions* of children; and, according to J. T. Rothrock, in preventing the so-called *urethral fever* induced in very susceptible males by the introduction of the catheter or bougie, it is very useful. The physiological action of the salt seemingly indicates that it is one of the remedies best suited for the treatment of *tetanus*. Clinical experience certainly accords with this conclusion: in a table published in previous editions of this treatise were collected thirty-four cases of tetanus, nearly all traumatic, treated chiefly by potassium bromide, with but four deaths. Not less than a half-ounce of the salt should be exhibited in the day, and at night hydrated chloral should be used as an hypnotic.

In *strychnine-poisoning*, Saisson has demonstrated the value of the bromide by experiments on animals, and Charles B. Gillespie



and C. L. Bard have each reported, under its use, recovery without vomiting after the ingestion of three grains of the alkaloid.

In nervous excitement connected with the *genital function*, the bromide is often of value. When there is actual inflammatory disease, as in *gonorrhœa*, the drug frequently fails to effect the desired end. If, however, there be no organic lesion of the organs or of their nerve-centres, the continued dose will usually succeed to a greater or less extent. We have found the remedy effective in cases of semi-impotence from over-irritability of the organs causing emission too soon during attempted sexual congress. There is abundant evidence as to its value in *nymphomania*. As an adjuvant to other physical and moral measures of relief, the salt may be used with satisfaction in men suffering from *masturbation*. In nervous symptoms occurring at the time of the menopause or complicating uterine disease, and in the peculiar train of morbid phenomena arising from the forced suppression of the sexual function in vigorous individuals of either sex to whom circumstances have denied marriage, the bromides have almost a unique power.

Bernard affirms that potassium bromide in doses of from twenty to forty-five grains a day removes with marvellous quickness *malarial enlargements of the spleen*.

**Administration.**—The action of bromine, whether combined with hydrogen to form hydrobromic acid, or with a base to form a bromide, is always the same, but the action is more or less modified according to the physiological effects of the base with which it is combined; thus, potassium having marked depressant action of itself upon the central nervous system, the potassium bromide is the most actively depressant of these salts. The ammonium radical is stimulating in its effect upon the spinal cord and therefore this salt is less useful as a spinal depressant than almost any other official bromide. Also the activity of the bromides probably bears a relation to the percentage of bromine in their composition; it is interesting to note therefore that calcium bromide contains eighty per cent. of bromine; sodium about seventy-seven per cent.; potassium salt about sixty-seven per cent., and the strontium bromide, sixty-five per cent.; a fluidrachm of the dilute hydrobromic acid is equivalent to about 8 grains of sodium bromide. For general purposes the sodium bromide is probably the salt of preference, although frequently the best results are obtained by combining several of the bromides.

When the bromides are used in chronic conditions it must be borne in mind that on account of their comparatively slow elimination there is a marked tendency for them to accumulate in the system and that therefore when used over long periods of time they must be given in much smaller doses than when used in a single dose. While it is perfectly safe to give one or two drachms of sodium bromide or even more at a single dose, in diseases of prolonged duration such as epilepsy this quantity cannot be exceeded in the twenty-four hours without danger of unpleasant symptoms. The action of the bromide,

as already mentioned, in the human being is less depressant upon the spinal cord than upon the brain, therefore, when this drug is used in the treatment of spinal convulsions such as tetanus or strychnine-poisoning, it is necessary to give very large quantities. In tetanus two to three drachms should be administered every two or three hours.

On account of the irritant action upon the stomach the bromides should always be given well diluted.

**Toxicology.**—So far as we know, no fatal case of acute poisoning by potassium bromide is on record. In our own experience an ounce taken by mistake by a young adult produced violent pain in the œsophagus, nausea with a little vomiting, great thirst, feeling of weight in the head, and excessive sleepiness, which lasted for three days. In a case reported by Dougall an ounce and a half taken within twenty-four hours was followed by coma, with weak pulse, cold extremities, temperature 96.8° F., total abolition of the reflex action, and general cutaneous anesthesia, followed by excessive drowsiness interrupted by periods of talking delirium and by periods of rationality, the symptoms gradually subsiding during a fortnight.

From the continuous employment of large doses of the bromide, however, when it is taken with sufficient freedom to accumulate in the system, a conjunction of phenomena known as *bromism* arises.\* The cerebral symptoms are a sense of mental weakness, heaviness of intellect, failure of memory, partial aphasia, great somnolence, and depression of spirits. With these there may be decided impairment of the sensibility of the mucous membranes and of the skin, so that titillation of the fauces may be without effect, and, according to Puche, even heat applied to the skin calls forth no complaint; Huette has seen in some cases absolute anesthesia of the sclerotic conjunctiva. The sexual function is abolished. There are also very generally fetid breath and an eruption of acne which may indeed be very severe. Of course, in any individual case of bromism many of these symptoms may be wanting; but when the use of the remedy is persisted in, they all at last become developed in an intense degree. In the words of Edward H. Clarke:

"The fetid breath becomes nauseous; œdema supervenes on congestion of the uvula and fauces; the whispering voice sinks into aphonia; sexual weakness degenerates into impotence; muscular weakness becomes complete paralysis; reflex, general, and special sensations disappear; the ears do not hear, nor the eyes see, nor the tongue taste; the expression of hebetude becomes first that of imbecility, then that of idiocy; hallucinations of sight and sound, with or without mania, precede general cerebral indifference, apathy, and paralysis; the respiration, without the stertor of opium or alcohol, is easy and slow; the temperature of the body is lowered; as the bromism becomes more profound, the patient lies quiet in bed, unable to move or feel or swallow or speak, with dilated and uncontractile pupils, and scarcely any change of the color of his skin or face."

\* Féré asserts that many of the disagreeable symptoms of bromism are due to its disturbance of the alimentary canal, and are prevented by the daily exhibition of four grammes of betanaphthol and four grains of bismuth salicylate, which doses are borne for months without any inconvenience, usually with much benefit to the appetite and digestion (*Nouv. Iconog. de la Salpêtr.*, 1890).

Death has been attributed to the continuous use of the bromide in large doses. Thus, Hameau reports the case of a young woman who took four and a half pounds during the course of ten months, and while in a condition of cachexia, with yellowish skin, a copper-colored eruption upon the forehead, colic, gastralgia, insomnia, etc., suddenly became greatly prostrated, and had delirium with profuse sweats, followed by death in four days. Anton Eigner details the case of a woman who took five pounds in less than a year, and while having very pronounced symptoms of bromism was seized with delirium and suffered from hallucinations of sight and hearing, saying that she was being poisoned, and finally died of pneumonia. In neither of these cases can it be considered probable that the bromide was the direct cause of death.

The symptoms of bromism usually disappear promptly with the withdrawal of the drug and leave behind no unpleasant sequelæ. Apparently the use of arsenic greatly lessens the liability to acne and it is frequently well, therefore, when using the bromides over long periods of time, to add one or two minims of the solution of potassium arsenite to each dose.

**BROMOFORM.**—*Bromoformum.*—*Formyl Bromide.*—This is a colorless liquid with an ethereal odor and sweetish taste, which, first brought forward in 1849 by Nunneley and Schuchard as an anesthetic, was found too dangerous for use as such, but has been employed to a considerable extent internally in the treatment of *whooping-cough* and other diseases for which the bromides are used. It is probably broken up in the system, but its products are eliminated with great slowness. It is undoubtedly capable of acting like the bromide, but has no advantage over the older preparations and is distinctly more dangerous. W. Gerhardt\* has shown that bromoform is capable of producing wide-spread fatty degeneration in the lower animals. E. Kiwull has collected twenty cases of poisoning by it; the symptoms have been pallor, titubation, dilatation of the pupil, coma, heart-failure, and collapse. The dose for the adult is six or seven minims (0.4 C.c.) in capsules.

Two substances, apparently parallel in that they are saturated solutions of bromine in oil and in that the bromine is stated to be in combination with olein, have been put upon the market by manufacturers, and are probably identical in their physiological influence.

*Bromolein* is a clear, yellow, oily liquid, said to contain twenty per cent. of bromine in oil of sweet almonds.

*Bromipin* is a similar liquid, prepared with bromine and sesame oil, and supplied to the market by the manufacturers in two strengths, one containing ten, the other thirty-three and one-third per cent. of bromine.

According to Merck's report, thirty grains of the stronger bromipin are equal to fifteen grains of potassium bromide; so that thirty grains of bromolein should be considered about equal to ten grains of potassium bromide. Of the weaker bromipin one-half ounce may be given as dose to the adult, representing theoretically twenty-four grains of bromide.

These substances may be used hypodermically, or may be employed, diluted with oil, endermically. After either method of administration bromine soon appears in the urine. They have been recommended by various clinicians in *epilepsy*, *insomnia*, *neurasthenia*, and other diseases in which the bromides are commonly employed. The dose of either substance appears to be in direct proportion to the amount of bromine contained.

\* See also *Wien. Med. Jahrb.*, 1883, 497. For poisoning, see *Times and Register*, 1892; also *Annals of Gynecology*, 1896-97; *Pest. Med.-Chir. Presse*, 1897.



**MONOBROMATED CAMPHOR.**—*Camphora Monobromata*.—This is a compound in which one atom of hydrogen in the camphor has been replaced by bromine. It occurs as a crystalline solid, or in large acicular crystals several inches long.

Our present knowledge of the physiological properties of bromated camphor rests upon the work of Bourneville, of Lawson, of Pathault, of Richard Peters, and of Pellicani. In frogs there is progressive loss of reflex excitability and of voluntary movement (Peters), which, according to Pellicani, is due to paralysis of the motor nerves. Death is caused by arrest of respiration (Peters). In mammals it produces violent convulsions, muscular weakness passing almost into paralysis, reduction of temperature (after small doses preceded by a rise—Peters), great decrease in the rate of the respiration and of the pulse (with occasional periods of hurried respiration—Peters), profound sleep or stupor, and finally death. Bourneville states that the blood-vessels of the eyes and ears are diminished in calibre. Upon man the drug probably acts as upon other warm-blooded animals; in a case reported by M. Rosenthal, forty-five grains of it caused tremblings, marked slowing of the pulse, and coma of six hours' duration.

Bromated camphor was first introduced by Deneffe as a nervous sedative, and as an antispasmodic, especially in *delirium tremens*, but is of little value; it is still used in *hysteria*, and has an especial reputation in *sexual excitement* and *spermatorrhæa*. It is taken with difficulty, and is likely to irritate the stomach. It is too irritant for hypodermic use. Dose, five to ten grains (0.3–0.6 Gm.), in capsule or coated pill, and repeated as necessary.

For a *résumé* of the physiological action of bromal hydrate, which is certainly valueless as a practical medicine, see the tenth edition of this treatise.

### NITRITES.

Although nitrous acid is itself not used in medicine all its salts as far as known have similar physiological properties.\* Apparently also the combinations formed by nitric acid and the polyatomic alcohols exercise the same effect upon the economy, probably being reduced in the system to nitrites. Four drugs belonging to this group are recognized by the U. S. Pharmacopœia.

*Amyl nitrite* is a yellowish oily liquid, extremely volatile, with a characteristic fruity odor, which results from the action of the nitric acid upon amyl alcohol. The Pharmacopœia directs that it contain about eighty per cent. of amyl nitrite.†

*Sodium nitrite* (this should be carefully distinguished from sodium nitrate) occurs in the market usually in white pencils; it has a mild saline taste and when exposed to the air deliquesces and is gradually oxidized into the nitrate. It is freely soluble in water.

*Ethyl nitrite* is official in the form of a four-per-cent. solution (*spiritus ætheris nitrosi*). This is a volatile inflammable liquid of a pale yellow color with a fragrant ethereal odor.

*Glyceryl trinitrate* or nitroglycerin, although being a salt of nitric acid, affects the system similarly to the salts of nitrous acid, probably

\* For evidence as to the physiological unity of the nitrites see G. A. Atkinson, E. T. Reichert (sodium nitrite), Richardson, Leech (ethyl nitrite), Brunton and Tait, Murrell and Hay, Henocque (nitroglycerin).

† *Berton's ether or tertiary amyl nitrite*, a mixture of amyl nitrite and iso-butyl nitrite, has been found by Lauder Brunton and T. J. Bokenham to act very much as does the ordinary amyl nitrite, except that its effects are somewhat more slowly developed and are more permanent. It is not proved to be more stable than the ordinary amyl nitrite and has no advantages over the latter. According to Dunstan, amyl nitrite of commerce is chemically a mixture of  $\alpha$  and  $\beta$  amyl nitrites, iso-butyl nitrite, ethyl nitrite, and propyl nitrite (*St. Bartholomew's Hospital Report*, 28, 1892).

being reduced in the body. It is official in the form of a one-per-cent. solution. Tablets of nitroglycerin, although not official, are largely employed. They are very likely however, to contain much less of the nitroglycerin than stated in the label, as this principle, being volatile, is largely evaporated unless they are carefully protected.

The nitrites are *incompatible* with antipyrine, the iodides, the bromides and ferric sulphate.

#### Official Preparations:

Amylis Nitris.....	1 to 5 minims (0.06–0.30 C.c.).
Sodii Nitris.....	1 to 3 grains (0.06–0.20 Gm.).
Spiritus Ætheris Nitrosi (4 per cent. Ethyl Nitrite).....	30 to 90 minims (2–6 C.c.).
Spiritus Glycerylis Nitratis (1 per cent. Nitroglycerin).....	1 to 3 minims (0.06–0.18 C.c.).

*Local Action.*—The nitrites are practically without irritating properties. They cause a progressive loss of functional power in every highly organized tissue with which they come in contact. Nerve-centres, peripheral nerves, muscles of organic and voluntary life, all succumb to them alike. If the contact be not continued too long, the tissue may recover even after a total suppression of its function,—a proof that the poison exerts no destructive chemical or devitalizing influence upon the tissues, such as that of sulphuric acid or veratrine.

*Absorption and Elimination.*—Amyl nitrite is absorbed with extraordinary rapidity, especially through the lungs, and must also be eliminated from or destroyed in the system with great rapidity on account of the fugaciousness of its action. F. Rohrmann believes that the nitrites undergo oxidation in the system, because he has found that when potassium nitrite is administered to the lower animals it appears in the urine as potassium nitrate.

*Physiological Action.*—The most prominent symptoms induced when amyl nitrite is inhaled by a man in moderate quantities are a sense of great fulness and distention of the head, amounting at last to severe pain, and accompanied by intense flushing of the face, a deep, labored respiration, and an exceedingly rapid, violent action of the heart. The succession of these phenomena is usually so rapid that often they seem to be simultaneous; but it is said that the cardiac disturbance is sometimes very distinctly manifest before the other symptoms. It has been noticed by Peck and confirmed by Ladendorf that objects look yellow to a person fully under the influence of the drug. After poisonous doses the symptoms have been great pallor, usually dilatation but sometimes contraction of the pupils, excessive muscular relaxation, slow, scarcely perceptible pulse, hemoglobinuria, and irregular respiration.

In the lower animals the first stage of the action is like that just described in man. After this the breathing becomes violently hurried and panting, progressive muscular weakness and diminution of reflex activity ensue, and finally death from failure of respiration, sensation and consciousness being preserved almost to the last. A very peculiar

symptom is that a long time before death both the arterial and the venous blood become of a nearly uniform chocolate color. Convulsions are sometimes present; but in our experience more often the animal is exceedingly quiet throughout the poisoning.

*Nervous System.*—The influence of the nitrites upon the cerebrum is very feeble, disturbances of intellection and of consciousness not being produced except by very decided toxic doses, and not being prominent symptoms of the poisoning. As was shown by H. C. Wood, the lessening of reflex activity and of voluntary motion which undoubtedly occurs in toxemia from these drugs is chiefly spinal in its origin, since after death the nerves and muscles preserve, though in an impaired condition, their functional power. On the motor centres of the cord the nitrite acts as a direct and powerful depressant, at the same time that it exerts a similar but much less pronounced influence on the nerves and muscles, decreasing, but not destroying, their functional life. The diminution of reflex activity is never preceded by a stage of functional excitement. In some animals convulsions do occur after amyl nitrite; but they are in all probability cerebral, not spinal, and due to the asphyxiating influence of the poison. Over the sensory nerves and centres the nitrites have but little power. They are among the last portions of the body to be affected, sensation being intact until near death: so that the drug is in no sense an anesthetic.

*Respiration.*—It is certain that the respiratory centres are greatly depressed by full doses of the nitrites, the breathing becoming both slow and shallow, and death finally occurring from centric paralytic asphyxia. Mayer and Friedrich assert that small doses of amyl nitrite increase the rapidity and depth of respiration by stimulating the respiratory centres; but this remains at present doubtful, it being probable that the increased respiration is secondary to the disturbance of the circulation, as is asserted by Winkler.

*Circulation.*—Although the pulse may be much increased in frequency sometimes from the very beginning by amyl nitrite, the arterial pressure is diminished, and finally is reduced almost to zero, the fall of pressure occurring equally after section of the vagi as at other times. As the number of heart-beats in the uninjured animal is increased rather than diminished, while the strength of the individual beat is not perceptibly lessened, it is evident that, at least in the early stages of the poisoning, the diminution of arterial tension is not cardiac in origin, but must be due to dilatation of the capillaries.

This conclusion has been confirmed by numerous experimenters.\* Although the question whether this vascular paresis is centric or peripheral cannot be answered definitely the effect is probably a direct action on the arterial walls.

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\* According to Bradford and Dean (*J. P.*, 1894, xvi, 34) and H. C. Wood, Jr. (*A. J. P.*, 1902, vi, 283) the nitrites cause a rise of pressure in the pulmonary circulation. The explanation of this phenomenon involves the disputed physiological question of the existence of a pulmonary vasomotor system and cannot therefore be taken up here.



Concerning the action of the drug upon the heart-muscle evidence is not convincing; although certain observers have claimed to have found some increase in the working power of the isolated frog's heart after small doses of the nitrite, others have failed to obtain evidence of such stimulation. If there is any direct stimulant influence upon the heart it is extremely slight, and only occurs after small doses; large quantities certainly depress the cardiac muscle as well as the vaso-motor system. The increase in the pulse-rate is owing to a paralysis of the cardio-inhibitory centres in the medulla.

That the fall of pressure is of vascular origin is shown by an experiment of Brunton, who found that if the descending aorta were tied high up, no perceptible



FIG. 11.—SHOWING EFFECT OF SODIUM NITRITE ON THE CIRCULATION.

It lowers the pressure by dilating the vessels and increases the pulse-rate by paralyzing the cardio-inhibitory centres. Time marker indicates 5 seconds.

fall of pressure was produced by the inhalation of the amyl salt until very late in the poisoning, when the heart itself was acted upon by the drug; also by the fact noted by Amez-Droz and by Gaspy, that the vessels of the rabbit's ear and of the frog's web can be seen to dilate when the salt is inhaled. In man the flushing of the face and of the retina, as noted by Charles Aldridge, indicates that the nitrite acts locally, probably upon some centre, before it does generally, as general dilatation of the vessels causes pallor.

An interesting question which here arises is, whether the dilatation is centric, due to an action on the vaso-motor nerve-centres, or peripheral, due to a direct action on the muscular coat of the arterioles. We believe that it must be peripheral, and not centric, in its origin, since in the experiments both of Brunton and of H. C. Wood it occurred after the arterioles had been separated from the vaso-motor centres by division of the cord.

Atkinson and D. J. Leech have each found that the nitrite enormously increases the flow of blood-serum which is being forced by a steady pressure through the

decapitated tortoise, or through a recently excised kidney; a solution 1 in 10,000 had a distinct effect in widening the blood-paths. In conclusion, it seems to us established that amyl nitrite does act locally on the coats of the arterioles, although it may at the same time influence the vaso-motor centres.

Bernheim, however, asserts that this cannot be so, and that the dilatation must be solely due to an action upon the vaso-motor centres, because he found that galvanization of the cervical sympathetic still caused contractions in the vessels of the ear of a rabbit to which amyl nitrite had been given. As pointed out by Pick, Bernheim's experiment does not warrant his conclusion. It only shows that the muscle-fibres in the walls of the vessels are not so completely paralyzed as to be unable to respond to very powerful stimuli. W. Filehne also dissents from the view that the action of the nitrite is upon the vessels. Filehne affirms that when to animals, whose lungs are exposed, inhalations of the nitrite were given, the change of color was not nearly so great as in the ears, and that if the sympathetic had been destroyed in the neck of a rabbit, and amyl nitrite exhibited, the vessels on the unwounded side actually became larger than those of the opposite ear. The answer to these results is, that opening the chest must derange most profoundly the pulmonic circulation, and that all observations upon the comparative size of vessels are very apt to be mere guess-work when the change is slight. Moreover, in Schuller's experiments, after destruction of the cervical sympathetic in a rabbit, inhalations of the nitrite produced still further dilatation of the vessels of the ear.

Filehne has by a single very ingenious experiment apparently shown that the acceleration of the pulse is due to a depressing influence upon the inhibitory centres. He divided the par vagum in a rabbit, employed an electric current to the severed nerves of sufficient strength to bring the pulse-rate to normal, and found that the nitrite was powerless to affect the rapidity of the cardiac action. Certain experiments performed by Mayer and Friedrich confirm that of Filehne. It is known that sudden asphyxia slows the pulse by exciting the inhibitory centre. Mayer and Friedrich found that this action is prevented by the inhalation of the amyl nitrite. Then, again, they found that when by compression of the arteries the blood was prevented from going to the head, the nitrite did not increase the rapidity of the pulse, and also determined that the reflex inhibitory slowing of the heart by irritation of a sensitive nerve is prevented by amyl nitrite. The sudden, thumping action of the heart which is, in man, so prominent a symptom of nitrite action is therefore probably, at least in part, due to depression of the inhibitory apparatus. There is, however, as pointed out by Reichert, some reason for believing that in small doses the nitrites act primarily as stimulants to the heart. Lauder Brunton long ago discovered that if the aorta be compressed so as to eliminate in great part the influence of the vaso-motor system, the nitrite causes a primary rise in the arterial pressure; and it is perfectly possible for an excessive heart-action to be more than neutralized, so far as the arterial pressure is concerned, by a vaso-motor depression, so that the immediate fall of pressure caused in the normal animal by the nitrite is not proof that the heart may not be stimulated. In G. A. Atkinson's experiments, 1 part of amyl nitrite in 20,000 produced a slight increase in the working power of the cut-out frog's heart (Williams's apparatus); 1 in 10,000 caused a rise for four or five minutes, followed by a fall; smaller and larger amount than these had either no effect or lessened the heart's action.\* It seems, therefore, that our present physiological evidence justifies the belief that very small quantities of the nitrites primarily stimulate the heart, although it is demonstrated that in moderate or large amounts the drug depresses or paralyzes the heart-muscle.

*Urine.*—F. A. Hoffmann found that in the rabbit a hypodermic injection of 0.111 to 0.113 gramme of amyl nitrite is enough to cause diabetes. If twice this amount of the amyl salt is used, the sugar

\* There is, however, still much uncertainty about the matter. D. J. Leech affirms that 1 in 10,000 always quickens and weakens the beat of the isolated frog's heart in a Roy apparatus. In a single experiment made with amyl nitrite on the isolated mammalian heart, Bock came to the conclusion that the amyl nitrite has no effect upon the heart itself. The experiment, however, does not seem to us sufficient, and the method employed is open to very grave objection.

becomes very abundant in the urine, and continues to be present for from twelve to thirty hours. Consentaneously with the elimination of sugar there is a great increase in the amount of the urine. The occurrence of glycosuria in man has not been recorded; it is produced by toxic doses only, if at all.

*Temperature.*—The nitrites, if given in sufficient amount, reduce most remarkably animal temperature. We have seen a pigeon perfectly conscious although its temperature had been brought down by this agent some 13° F. This influence is as marked in fever as in the normal condition of the animal, and is independent of the nerve-centres, occurring after section of the cord, and even after death in those cases in which post-mortem rise or continuance of high temperature normally takes place. We have also experimentally determined that it is associated with diminished excretion of carbonic acid. It must therefore be due to a direct arrest or check of tissue-changes or oxidation within, or without, the blood. This is probably connected with the changes caused by the nitrites in the hemoglobin. After large doses of the nitrites the blood in both arteries and veins assumes a uniform chocolate-brown color. This is due to the formation of a new chemical compound, probably methemoglobin. This substance is a much more stable body than oxyhemoglobin, that is, it gives up its oxygen much less readily to the tissues. Although the oxygen-carrying power of the blood is much reduced in nitrite-poisoning, Gamgee has shown that it is not entirely lost, nor are the corpuscles of necessity permanently injured. The mouth-temperature in man is certainly sometimes elevated by the inhalation of amyl nitrite, but the rise is a very temporary one. W. A. Manassein and N. Sassezki found, in a number of studies upon normal and fevered men, that while the peripheral temperature was at first increased the rectal temperature was always reduced, and after a time the surface of the body grew cooler. The maximum reduction was reached in one to one and a half hours, and in a case of fever amounted to 3° C.

The first to describe the chemical changes in the blood was Gamgee. He believed the new compound to be a nitrite-oxyhemoglobin, but it has been considered by most observers, on account of similarity of spectrum, to be the methemoglobin of Hoppe-Seyler. Haldane, Makgill, and Mavrogordato assert, however, that the spectra are not absolutely identical, and that the new compound is really a mixture of nitric-oxide-hemoglobin and hemoglobin.

Gamgee showed conclusively that the new compound in the blood yields oxygen to a reducing agent, and that when nitrite blood is brought into contact with prepared guaiacum-paper it still oxidizes it, though not so actively as normal; so that evidently the blood-corpuscles retain to a greater or less degree their power of yielding ozone to bodies desiring it, and are capable of exerting at least this portion of their respiratory function: further, when this ozone is given up and the oxyhemoglobin changed into hemoglobin, so far as our present knowledge goes, the hemoglobin must absorb more oxygen before it can unite with the nitrite. Evidently, then, absorption of oxygen must take place; evidently the blood-corpuscles must perform their respiratory function; but evidently also they are greatly crippled and impaired in the rapidity and ease of its performance.

Haldane, Makgill, and Mavrogordato found that when an animal is placed in oxygen gas, under a pressure sufficiently high to so saturate the serum of the blood



with oxygen that it (the serum) was able to maintain life, ordinarily fatal doses of the nitrites failed to kill, although by increasing the amount of the nitrite death could be produced; evidence that the influence of the nitrites upon oxidation is an important but not a sole factor in their toxic influence. Further, Gamgee showed that potassium and other nitrates act upon the blood as do the nitrites, yet the symptoms caused by them are very different from those produced by the nitrites. It is also sure that various drugs in toxic doses check oxidation, but do not cause the same symptoms as are produced by the nitrites; finally, when arrest of oxidation in the body is caused by substituting oxygen by an inert gas, such as nitrogen, the symptoms are essentially different from those of nitrite-poisoning, the brain and consciousness being always affected before the spinal centres, whereas under the influence of amyl nitrite the contrary occurs.

In sufficient dose amyl nitrite is poisonous to the white corpuscles; Atkinson has found that 1 in 1000 kills the corpuscles in from fifteen to twenty minutes.

**SUMMARY.**—The dominant physiological action of the nitrites is upon the spinal cord and the circulation. Under their influence arterial pressure falls from paralysis of the blood-vessels, chiefly due to a direct action upon the muscles in their walls. At the same time the vagi-centres are paralyzed and the heart is stimulated directly or indirectly, the number and force of its contractions being increased, this period of stimulation after moderate doses gradually subsiding into the normal state, but after toxic doses passing into one of cardiac paralysis, with a final arrest in diastole, which is due to a direct action upon the heart-muscle or contained ganglia. Paralysis of motion and loss of reflex activity, prominent phenomena of advanced poisoning, are due to a direct action upon the motor side of the spinal cord. Death results finally from paralysis of the respiratory centres. By a direct action upon the red blood-corpuscles the hemoglobin is converted into a new compound, probably methemoglobin. The fall of the bodily temperature is probably the result of lessened oxidation. Locally applied in concentrated form, the nitrites paralyze all higher tissues.

**Therapeutics.**—The nitrites are employed to meet indications which are very closely in accord with their known physiological action. When an extremely prompt but not lasting effect is desired amyl nitrite should be chosen. Thus by virtue of its antispasmodic effects it may be of service in certain forms of epilepsy. In a fully developed paroxysm of *epilepsy* it must be used with caution, because the patient's condition will obscure its early effects; but in the *status epilepticus*, when there is an almost indefinite repetition of the fits, the remedy may be of great use in stopping the convulsions. When there is a notable interval in ordinary epilepsy between the aura and the convulsion, the latter can usually, if not always, be entirely prevented: the patient should carry a small vial containing a few drops of the drug or so-called "pearls" (minute flasks, each containing five minims, which are to be broken in a handkerchief), and should inhale the amyl salt so soon as the aura is felt.

S. Weir Mitchell calls attention to the value of the nitrite as an aid in diagnosing those occasional cases of nervous disorder in which

*petit mal* is simulated by attacks really due to passing congestion of the nerve-centres. He asserts that in these cases amyl nitrite instead of arresting the paroxysm increases its severity.

In nervous *spasmodic dysmenorrhæa*, it is stated by various authorities that inhalation of amyl nitrite will sometimes bring immediate relief, two to six minims being given when the pain comes on, and repeated *pro re nata*. As was first pointed out by William F. Jenks, the nitrite is most effective in arresting *puerperal convulsions*, but if the convulsions occur shortly after parturition the use of the nitrite is attended by the greatest danger of producing uterine relaxation and serious or even fatal post-partum hemorrhage.

Amyl nitrite is a very valuable remedy in the treatment of *tetanus* and of *strychnine-poisoning*. In the experiments of St. Clair Gray, which have been substantially confirmed by Hobart A. Hare, although one-quarter of a grain of strychnine was found to be sufficient to cause death in an immediate convulsion in the rabbit, no decided symptoms whatever were induced in two rabbits by the subcutaneous injection into each of half a grain of strychnine with ten drops of the nitrite. During a paroxysm of cramp asphyxia from strychnine, the poison of tetanus, or other similarly acting cause, the nitrite should be given hypodermically, the lack of respiratory movement interfering with its absorption through the lungs. In cases of *uremia*, or *puerperal eclampsia* one of the more persistently acting salts, as nitroglycerin, should be chosen.

During the algid stage of an ordinary *intermittent fever* amyl nitrite will put an end immediately to the chill, but does not affect the development of the hot stage. It might possibly be of service in the algid stage of a *pernicious malarial fever*.

Led by the evidences of arterial spasm in the sphygmographic tracings in a case of *angina pectoris*, Lauder Brunton in 1867 suggested its use in that disease. As the pathology of these cases of heart-pang is not definitely made out, it seems useless to speculate how the nitrite acts in many cases; but there is abundant evidence of its value in relieving, almost instantly, agony which has resisted all other treatment. This appears also true whether valvular disease or merely functional disorder exists. Foster has found the drug of great service in aortic insufficiency with excessive hypertrophy and severe frontal headache.

The nitrites, especially nitroglycerin, have been largely used in various forms of sudden *heart-failure*, even when such failure is dependent upon fatty degeneration or other disease of the heart itself. The direct stimulant influence, if it exist at all, of the nitrite upon the heart is, however, of the briefest duration, and if the least overdose of the drug be given, passes into cardiac depression. The zone between stimulation and depression of the heart is so narrow that the greatest care must be exercised whenever there is any cardiac disease, or whenever the heart is violently depressed by such a poison as chloroform. Although Reichert states that he has seen the blood-pressure

and pulse-wave, which had been depressed almost to zero by ethylene bichloride, greatly increased by amyl nitrite, in an elaborate series of experiments made by H. C. Wood with chloroform no such effect could be obtained. Moreover the widening of the blood-vessels will certainly tend to further lower the pressure. It is probable that the nitrites do harm rather than good in these conditions.

Its physiological action would indicate that it should be of service in all cases of spasm of the capillaries, of the bronchial tubes, and of the muscular system generally.

Amyl nitrite is of very great value for the purpose of relaxing spasms; it will usually abort a paroxysm of *asthma*, but in practice it will be found that the asthmatic patient becomes so rapidly accustomed to the use of the drug as to make it of comparatively little value.

Whenever for any reason it is desired to dilate the blood-vessels the nitrites are our most certain, in fact almost our only certain remedies. They are very largely used in cases of habitual high arterial pressure, especially in *arterial fibrosis* in which the increased peripheral resistance is developing, or has produced, increased cardiac power. In some cases of *acute apoplexy* with high arterial pressure they might be of great service. Oscar Berges and others have used amyl nitrite with good effect in migraine with capillary contraction.

**Administration.**—The choice of the nitrites is governed almost solely by the quickness and duration of action desired. The effects of amyl nitrite come almost instantly and last from five to ten minutes. According to Koreynski the maximum effect from nitroglycerin appears in from three to five minutes and disappears in about three quarters of an hour. Leech states that the effects of ethyl nitrite may endure for two hours. Sodium nitrite probably maintains its action for about the same length of time. Where it is desired to make a continuous impression on the system, the nitrite must be frequently repeated; the common custom of giving nitroglycerin three times a day is silly.

Amyl nitrite is usually employed by inhalation, from one to three or five drops being placed on a handkerchief and held near the mouth or nose, the handkerchief being removed so soon as a sense of fulness of the head is experienced. We have given it by the mouth, dropped upon sugar and taken instantly in doses of two or three drops.

Nitroglycerin may be given by the mouth in the form of the official solution, or it may be injected hypodermically. Sodium nitrite should always be dispensed in solution on account of its deliquescence. There is not at present sufficient evidence to enable us to decide as to the maximum amount of the drug which it is safe to give. In a case of cholera, D. B. Smith exhibited hypodermically two drachms in the course of an hour and thirty-six minutes without inducing any serious symptoms, and a dose of a dessertspoonful has been recovered from,\* emetics being given. Doses of six to ten grains of sodium



nitrite (G. A. Atkinson) in man sufficed to raise the pulse to 110 or 120, with flushing of the face and intra-cranial throbbing; the symptoms usually began in twenty minutes and lasted several hours, and were in no case disagreeably severe.

Of the spirit of glyceryl nitrate a single drop is said to have caused insensibility, and in the case of Mr. Field, who took two drops, loss of consciousness and of the pulse at the wrist was complete. J. Noer attributed the following symptoms in a woman to the use of ten-drop doses of the alcoholic solution of nitroglycerin: The pulse was slow, intermittent, and very irregular, the pupils dilated, the urine scanty and containing considerable pigment. There were also pain in the region of the heart, intense headache, sense of constriction around the forehead, and great weakness of the muscles.

**Toxicology.**—We know of no deaths recorded from amyl nitrite, though very alarming symptoms have resulted in various cases. Ten minims of a ten-per-cent. solution, hypodermically injected, are said to have been followed by two successive furious epileptic convulsions, each preceded by arrest of respiration and of the heart's action, to which arrest they were probably due.\* Three drachms caused no other symptoms than violent vomiting. One drachm occasioned great weakness, cyanosis, and very feeble, slow, intermittent pulse. Two drachms caused vomiting within five minutes, great weakness of the pulse, slow respiration, temperature below 95° F., semi-coma, with hemoglobin, but no sugar or blood-corpuscles, in the urine for twelve hours after the poisoning.

The best treatment for the poisoning would consist in favoring vomiting by apomorphine or other agents, and the use of artificial respiration and hypodermic injections of strychnine and digitalis.

**Erythrol Tetranitrate.**—A crystalline solid which, when pure, is colorless, but which is prone to decomposition and to become yellow. It is a violent explosive whose trituration has caused death. It is slightly soluble in water, but readily in alcohol. Its physiological action appears to be entirely parallel to that of glonoin, excepting in that its influence is less powerful and is much more prolonged. In man its effects are said not to be apparent in less than half an hour and to last for more than an hour. It has been especially recommended in the treatment of *angina pectoris*. As its alcoholic solution is explosive, it should always be used in tablets, whose preparation requires great care. Dose, from one-half to one grain (0.03–0.06 Gm.).

## LOBELIA.

The leaves and tops of the *Lobelia inflata*, an herbaceous annual found throughout the eastern portion of the United States, producing pale or yellowish-green flowers in racemes. The dried plant has a slight irritating odor and a taste at first scarcely perceptible, afterwards burning, acrid, and attended by a flow of saliva. Proctor discovered the alkaloid *lobeline*, which was long believed to be

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\* Strahan (*Journ. Ment. Sci.*, xxx, 252), J. Roese (*Centralb. f. Klin. Med.*, 1888), George E. Shoemaker (*Med. News*, 1893, i.), and Stansfield (*Brit. Med. Journ.*).

liquid, until J. U. and G. G. Lloyd obtained it in broad, colorless, odorless, and tasteless crystals.\*

#### Official Preparations :

Fluidextractum Lobeliæ.....	1 to 5 minims (0.06-0.30 C.c.).
Tinctura Lobeliæ (as an emetic 1 fluidrachm, 4 C.c.).....	20 minims (1.3 C.c.).

**Physiological Action.**—Upon the lower animals lobelia produces, after a primary stage of motor-cord stimulation, progressive failure of motor power which is due to a paralyzing effect upon the peripheral endings of the motor nerve. According to Dreser when the nerves are protected from the action of lobelia there is evidence of a stimulation of the spinal cord. According to some observers there is produced by a moderate dose, a primary excitation of the respiratory centre and also of the vomiting centre, which is followed by a paralysis of respiration. Its effects upon respiration are so much more powerful than upon the motor nerves that its action in mammals as a motor paralyzant is of little importance. Dreser also found that there was a palsy of the pneumogastric terminals in the bronchi.

According to both Ott and Afanasieff, lobelia produces a rise of the arterial pressure which occurs after section of the cord. Ott believes that the effect is a direct one upon the muscles of the arterial walls; on the other hand, in the experiments of Afanasieff, lobeline caused in the frog's heart a period of increased work, followed, if the dose were large enough, by loss of power ending in diastolic arrest. In the later stages of lobeline-poisoning the arterial pressure falls progressively, so that it is probable that lobelia first stimulates and afterwards paralyzes both the heart and the arteries. A very important point to be noted is that the action of lobelia upon the circulation is entirely subordinate to its influence upon the nerve-centres, especially upon respiration, and is, therefore, of no value to the therapist.

**Therapeutics.**—The former use of lobelia as an emetic, and for the purpose of relaxing spasm in various diseases, has been entirely superseded by more effective and less dangerous remedies. Lobelia remains, however, a valuable drug in the treatment of *asthma*, or acute *bronchitis* with *bronchial spasm*, in which it may be given in small repeated doses at long intervals, or in severe attacks every few minutes until nausea is induced. An infusion (one ounce to a pint) has been strongly recommended as a local application in the *eczema* produced by the *Rhus toxicodendron*, or "*poison-vine*." The dose of the tincture, as an expectorant, is twenty to forty minims (1.3-2.5 C.c.); in the paroxysm of asthma, one-half to one fluidrachm (2-4 C.c.) every half-hour until nausea is induced. According to S. Nunes, from five to forty centigrammes of lobeline may be given a day, but in any case the first dose should not exceed one-fortieth of a grain, to be increased *pro re nata*.

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\* The Messrs. Lloyd also assert that there is a second alkaloid in lobelia, but the researches of Dreser render it probable that this second alkaloid is a derivative from lobeline.

**Toxicology.**—The symptoms produced by large doses of lobelia in man are nausea, soon followed by violent vomiting, accompanied by intense prostration, as is shown by feeble pulse, cold sweats, pale skin, and great muscular relaxation. Purging may or may not occur. Numerous cases of fatal poisoning by it have been recorded. The symptoms are those above mentioned, intensified; in some cases vomiting does not occur, and it is especially under these circumstances that fatal effects have been noted. Burning in the fauces and œsophagus, and epigastric distress, in addition to the intense prostration, bordering upon collapse and finally merging into complete collapse, with coma, stupor, muscular tremblings, and in some cases convulsions, precede the fatal termination.

The treatment should consist in washing out the stomach with plenteous draughts of a warm solution of tannic acid, in the free exhibition of opium, alcohol, ammonia, strychnine, and digitalis and in the use of external stimulation by dry heat, frictions, mustard, etc., precisely as in poisoning from *veratrum viride*.

### GELSEMIUM.

The rhizome and root of *Gelsemium sempervirens*, the *yellow* or *Carolina jessamine*, a beautiful climbing plant of the Atlantic Southern United States, distinguished by its large, axillary, very fragrant, clustered blossoms and perennial dark green leaves. According to Cushny gelsemium depends for its activity chiefly upon *gelseminine*; the alkaloid *gelsemine* which was discovered by Wormley being comparatively feeble in its action. The very light, fibrous, dirty yellowish root has a bitterish taste.

#### Official Preparations :

Fluidextractum Gelsemii. ....	3 to 5 minims (0.2–0.3 C.c.).
Tinctura Gelsemii (10 per cent.).....	15 to 30 minims (1–2 C.c.).

**Physiological Action.**—Gelsemium produces in the lower animals symptoms similar to those which it causes in man, with the exception that convulsions are very generally developed.

The convulsions are not always present, but they have been observed in the frog, pigeon, cat, rabbit, and dog. The loss of voluntary power precedes the convulsions, and in the careful experiments of Ringer and Murrell upon frogs it was found that the cord was rapidly exhausted by repeated irritations, so that convulsions could not at once be induced. Bartholow states that in the rabbit, cat, and pigeon the convulsive movements are backward, sometimes amounting to complete somersaults.

**Nervous and Muscular Systems.**—In large doses gelsemium causes increased reflex activity and even tetanic convulsions by its stimulating effect upon the spinal cord. If the dose has been large enough this condition of motor excitement gives way to one of paralysis which is probably due to the effect both upon the spinal cord and the peripheral nerves.



The alkaloids gelsemine and gelseminine differ very markedly in their physiological effects. Gelsemine is primarily a stimulant to the motor cord (Ott and Taylor) and in large doses a paralyzant to the peripheral ends of the motor nerves. According to Cushny, the failure of Bartholow, of Ringer and Murrell, and other investigators to obtain evidence of the motor-nerve paralysis is due to the fact of their having used insufficient doses.

Gelseminine on the other hand appears in no dose to act as a spinal stimulant, but causes in both the frog and the rabbit, according to Cushny, a gradually increasing paralysis by a depressant action upon the motor ganglia of the spinal cord. After very large doses this alkaloid also depresses the peripheral motor nerves.

*Respiration.*—Gelsemium usually kills by a paralysis of respiration. According to the researches of Burdon Sanderson and of Ringer and Murrell, immediately after the ingestion the extent of the respiration, but not its rate, is increased; very shortly, however, both rate and depth enter a condition of progressive palsy ending in death. The respiratory changes are the product of a direct action upon the respiratory centres, being uninfluenced by previous section of the vagi.

*Circulation.*—The action of moderate doses of gelsemium upon the circulation is not pronounced, but the toxic dose depresses both the pulse-rate and the pressure. As this occurs after previous section of all the cardiac nerves and the spinal cord (Ott), it is probable that the poison exerts a direct influence upon the heart. How far or in what way it affects the arterial system we have no knowledge.

*Eye.*—Ringer and Murrell affirm that decided non-toxic doses of the drug cause contraction of the pupil. However this may be, marked dilatation of the pupil is a very constant symptom in the poisoning, and the local application of gelsemine to the eye produces violent mydriasis, with paralysis of accommodation.

It would seem probable that the mydriasis is due to an action upon the peripheral nerve-endings in the eye. The palsy of the external rectus and the ptosis indicate that such action is paralytic, so that it is a probable conclusion that peripheral oculo-motor paralysis is the cause of the dilatation of the pupil. The falling of the jaw and the loss of the power of articulation indicate that all the motor nerves of the head are acted upon by the poison.

*Therapeutics.*—Gelsemium was originally employed as an arterial sedative and febrifuge in the *malarial fevers* of the South, and subsequently in other *sthenic fevers*. It appears in some way to depress the bodily temperature, but certainly possesses no controlling influence over the arterial system at all comparable to that of *veratrum viride* and *aconite*. Bartholow commends it highly in *pneumonia* and *pleuritis*; its influence for good in these disorders would seem, however, to be chiefly associated with its power of lessening the rapidity of respiration and increasing the tendency to perspiration. It does not appear probable that any advantage to be derived from it will counterbalance the dangers attending its employment in the large doses required. In *asthma*, *spasmodic laryngitis*, *whooping-cough*, and *nervous cough*, in which it is also recommended by Bartholow, its employment seems more plausible, as in these cases there is a distinct spasmodic element. The testimony to its value in cases of *trigeminal*,

*ovarian*, and other *neuralgias* is strong. How it does good in these disorders is as obscure as is the nature of the neuralgias, and in our hands it has usually failed. The marked effect of the drug upon the facial nerves would appear to indicate its employment in facial neuralgias, and especially in facial spasmodic affections. In acute *mania* the drug may be employed in full doses as a calmate.

**Toxicology.**—The earliest symptom of gelsemium-poisoning is a feeling of languor which is soon followed by dizziness and disturbance of vision, with, in some cases, a pain over the brows. Ringer and Murrell state that the pupil is contracted, but this is probably an inconstant result. Later the muscular weakness is extreme, and in several cases the flexors of the arms have been especially affected. The disturbance of sight is now very marked; double vision, or partial or even complete blindness, may exist; the pupil is widely dilated and immovable; the external rectus muscle is weakened, sometimes sufficiently to produce a marked internal squint; the eyelid droops, and is raised with difficulty or falls in paralytic ptosis. If the patient is able to walk at all, the gait is staggering; the jaw drops, articulation fails; the general sensibility is much impaired; the respiration slow and labored; the pulse feeble and thready; the skin bathed in a cold sweat; the bodily temperature greatly lowered. Sometimes drowsiness is felt after moderate doses of the poison, but consciousness may be preserved in the midst of very severe symptoms, although in all the fatal cases whose record we have met with it has been lost before death. The drug acts very promptly, symptoms usually appearing in about twenty minutes and beginning to subside in two or three hours. I. Ott has collected six cases of fatal poisoning, a teaspoonful of the fluidextract being the smallest amount that has caused death in the adult. Wormley believes that his chemical examinations have shown that in one fatal case the fluidextract ingested could not have contained more than one-sixth of a grain of the alkaloid.

The *treatment* of gelsemium-poisoning should be conducted on general principles. Our present knowledge does not indicate that morphine and gelsemium are physiological antagonists, but George S. Courtright asserts that they have such relation, and details a case in which recovery occurred after the ingestion of from one to two teaspoonfuls of the tincture, one and one-half grains of morphine having been given hypodermically and one grain by the mouth.

**TABACUM.**—*Tobacco* is no longer recognized by the United States Pharmacopœia, and is not at present used in practical medicine. We shall here discuss it very summarily, referring the reader to the tenth edition of this treatise for a more elaborate study of its physiological action.

Tobacco depends for its activity upon the presence of an alkaloid, *nicotine*, a poison of such intensity that it has caused death in three minutes. The fatal dose of nicotine has not been made out. One-thirty-second of a grain will cause serious symptoms; one-seventh of a grain has been recovered from. The symptoms produced by tobacco in those unaccustomed to its use are horrible nausea and vomiting, giddiness, intense malaise, with weakness, followed, if the dose has been sufficient, by burning pain in the stomach, purging, free urination, extreme giddiness passing

into delirium, a rapid, running, and finally imperceptible pulse, cramps in the limbs, absolute loss of muscular strength, a cold, clammy skin, and finally complete collapse, terminating in death.

In the lower animals, especially in the frog, to the symptoms commonly seen in man are added violent convulsions, which are of spinal origin and are followed after a time by paresis, which is probably also in part of spinal origin, although it has been demonstrated that tobacco is a powerful *depressant to the motor or efferent nerves*, acting primarily upon their peripheral filaments. The afferent or sensory nerves are much less affected than the motor, but are probably also depressed. The sympathetic ganglia are first stimulated and then depressed by nicotine. To these actions are probably due the increase of saliva and other secretions caused by small doses and the lessening of gland activity produced by large doses. Upon the voluntary muscles the drug has no action.

Upon the circulation nicotine has a very distinct influence, producing first rise and afterwards fall of pressure. The rise of pressure is certainly in part due to stimulation of the cardiac muscles or ganglia, but probably is also in part the outcome of peripheral contraction of the vessels; and it is further probable that the final paralysis is due to a double depressing influence upon the heart and the arterial walls, although these points have not been distinctly proved.

Upon the pupil nicotine acts as a myotic, probably paralyzing the peripheral ends of the sympathetic, and almost certainly stimulating the oculo-motor nerves.

The only use now made of tobacco in medicine is in the preparation of ointments for painful *hemorrhoids*, and in the form of a strong wash for *pruritus*. Its free external use is always accompanied by danger, and has caused death.

The dose of tobacco is five grains (0.3 Gm.), in infusion.

**Toxicology**—A large number of deaths have resulted from the medicinal use of tobacco, Husemann stating that no less than ten fatal cases have been caused by tobacco enemata alone. Copland has seen a clyster containing half a drachm produce death. Even smoking has caused an acute fatal poisoning. Melsens affirms that the smoke of half an ounce of strong tobacco contains sufficient nicotine to prove fatal.\* In the only case of criminal nicotine-poisoning on record, an unknown amount of the alkaloid was forced into the mouth of the victim, causing death in from three to five minutes. The treatment of tobacco-poisoning consists in washing out the stomach, the free administration of ammonia and alcohol, the hypodermic use of moderate amounts of strychnine, and the employment of such external measures as dry heat, rubbings, etc. If these fail, artificial respiration should be maintained. The excessive use of tobacco produces in some persons serious nervous disturbance, such as insomnia, irritability, general feebleness; the most characteristic symptom is a peculiar irregularity of the heart's action, often accompanied by distinct intermissions. Amaurosis is also sometimes present.† Jonathan Hutchinson affirms that he has seen this amaurosis recovered from under the use of opium and champagne without the abandonment of the habit of smoking. We have seen impotence as the only distinct symptom of chronic tobacco-poisoning.

### CONIUM.

The U. S. Pharmacopoeia recognizes only the full-grown fruit, gathered while green, of *Conium maculatum* or Water Hemlock. The plant is umbelliferous, a native of Europe, but naturalized in the United States. The fruits are one to two lines long, roundish-ovate, striated, with five crenated ribs on the outer sides of the easily

\* For a number of cases, see Stillé's *Therapeutics*, ii. 374.

† The diagnosis of tobacco amblyopia depends upon the history of the abuse of the drug, the failure to improve with optical therapeutics, and the presence of a scotoma, usually oval in shape and negative in character, particularly pronounced for red and green, while the periphery of the field of vision remains unaltered. If, in addition, there is a quadrant-shaped patch of atrophic pallor in the nerve-head, the diagnosis becomes still more certain. Atrophy of the nerve may result, but in many cases there is no structural change, as the symptoms may go off in a few hours (De Schweinitz's *Toxic Amblyopia*).



separable halves, and have a peculiar mouse-like odor. Conium is famous in history as the penal poison of the Greeks, with which Socrates was killed. The active principle is *coniine*, a yellowish, oily, liquid alkaloid, highly volatile, of a strong odor similar to that of the urine of mice, and of a very acrid taste. It is freely soluble in alcohol and in ether, and slightly so in water, with which it forms a hydrate, and it coagulates albumin; when exposed to the air it undergoes decomposition, becoming first brown, afterwards resinous; heat accelerates the change. The U. S. Pharmacopœia directs that 0.5 per cent. of the alkaloid shall be present in the drug.

### Preparation :

Fluidextractum Conii..... 1 to 3 minims (0.06–0.18 C.c.).

The extract was formerly official but is no longer recognized, the dose of it was  $\frac{1}{2}$  to 1 grain (0.03–0.06 Gm.). Coniine Hydrobromide is occasionally employed in doses of  $\frac{1}{32}$  to  $\frac{1}{16}$  grain (0.003 to 0.005 Gm.).

*Local Action.*—Upon the mucous membranes conium acts as an intense irritant. In a concentrated form it is probably fatal to all highly organized tissues, Christison having proved this to be true in regard to the muscles which are not influenced by the alkaloid taken internally.

*Elimination.*—It is absorbed with great rapidity, and escapes through the system chiefly if not solely through the kidneys. Zaleski and Dragendorff have found it abundant in the urine during the first twelve hours of the poisoning; Prevost has seen the urine of poisoned animals cause in a frog the characteristic general palsy, and in a doubtful case of poisoning this physiological test might decide the diagnosis.

*Nervous System.*—The retention of consciousness and all the mental faculties almost up to death in conium-poisoning shows that the drug has but little influence upon the general cerebral cortex. According to Lautenbach, the convulsions which occur in the lower animals are, however, of cerebral origin, since after division of the cord they were confined to those portions of the body situated above the section. They are probably asphyxial or of other secondary character.

The characteristic effect of conium is an ever increasing muscular weakness. This is due chiefly to a paralysis of the peripheral endings of the motor nerves although there is evidence that the spinal cord is also affected. The drug seems to exercise a similar paralytic influence on the sensory nerve-endings but much less powerfully. In mammals respiratory failure, probably due to palsy of the phrenic nerve, usually leads to the death of the animal before the other motor nerves are completely insensible to electrical stimulation.

The original discovery of Kölliker, that the paralysis of coniine-poisoning is due to paralysis of the efferent or motor nerves, has since been abundantly confirmed.

Kölliker demonstrated that in the poisoned frog immediately after death the galvanic current applied to the nerve is powerless to induce contractions; that if by tying the aorta access of the poison be cut off from the hind legs, there is a stage of

the poisoning in which galvanic stimulation of the nerve of the front leg fails to affect the tributary muscles, although it does produce reflex contractions in the hind legs; proof that the anterior afferent nerves and the spinal cord still retain functional activity after this activity has been lost in efferent nerves reached by the poison. These experimental results have been confirmed by Funke, by Guttmann, and by Pelvette and Martin-Damourette. These last-named observers also noted that when coniine and strychnine were given simultaneously to a frog from one of whose sciatic nerves the circulation (*i.e.*, direct access of the poison) was cut off in either of the manners spoken of, they produced by their conjoint action a commingling of paralysis in all other parts of the body with violent tetanic spasms in the protected leg,—a commingling explainable only on the supposition that the coniine paralyzed all the motor nerves to which it had access through the circulation. These experiments upon the frog have been confirmed by B. F. Lautenbach, Verigo, A. W. Hofmann, Prevost, H. Schultz, and Fliess. Hayashi and Muto have shown that, although the nerves of purely voluntary motion are acted upon in the mammal by coniine, the phrenic nerve, at least in the rabbit, is even more susceptible to its influence.

It has been generally believed that coniine does not affect the sensory nerves, but the evidence appears to show that this is not correct; only that the action upon the sensory nerves is so much less decided than that upon the motor fibres that it counts very little in the general influence of the drug.

In 1875 Gubler called attention to the local influence of conium in benumbing the cutaneous sensibility, and Lautenbach found that when he tied the abdominal aorta and left axillary artery in the frog, and then injected a dose of coniine into the abdomen, irritation of the leg whose nerve was not protected from the poison failed to cause reflex movements at a time when irritation of the protected nerves produced reflex actions in distant parts of the body.

The exact influence of coniine upon the *spinal cord* cannot yet be considered absolutely determined, but it is most probable that the poison has a feeble depressant action. Verigo asserts that it is a powerful spinal depressant, and Pelvette and Martin-Damourette say that it acts as an excitant. Lautenbach, in carefully investigating the subject, failed to obtain, under any circumstances, evidences of excitement of the cord; he did succeed in producing loss of reflex activity when the nerve was protected by tying the artery in the limb, but, as in all but two of fifty-two experiments the reflexes in the protected limb were not greatly reduced until just before death, it is plain that any action upon the spinal cord is unimportant and dominated by the more powerful peripheral influences of the poison.

*Muscles.*—All observers agree that in conium-poisoning the muscles themselves are not affected.

*Pupil.*—The pupil is generally dilated by coniine; but both Von Praag and Verigo assert that the phenomenon is not constant, at least in animals. The ptosis of conium-poisoning indicates that the dilatation of the pupil is due to oculo-motor paralysis. The known action of the drug upon nerve-trunks indicates that this paralysis is peripheral,—a conclusion corroborated by the experiments of I. Hoppe and of Lautenbach, each of whom found that when coniine is dropped into the eye of an animal it causes at first contraction, apparently due to the intense irritation, and afterwards dilatation, of the pupil.

*Temperature.*—Verigo, Von Praag, and others affirm that lethal doses of conium cause a decided lowering of temperature; but Lautenbach asserts that the drug decidedly increases the temperature both when in therapeutic and when in toxic doses.

*Circulation.*—No sufficient investigation has as yet been made upon the action of coniine upon the circulation. Lautenbach states that the arterial pressure falls immediately after the injection of coniine, and afterwards rises far above the normal point, and that the pulse is at first accelerated, but afterwards retarded. The secondary rise of pressure is probably due to asphyxia. The primary pulse-acceleration is explained by the observation of Pelénard (confirmed by Prevost) that the pneumogastrics are paralyzed before the motor nerves. Prevost finds that the heart itself is scarcely affected by the poison.

**SUMMARY.**—The chief symptom of poisoning by conium is a failure of voluntary and involuntary movement, the result of a progressive paralysis of the motor nerves. The cerebrum is not affected, hence consciousness is preserved to the last. The pupil is dilated by a peripheral paralysis of the oculo-motor nerve. The sensory nerves and the spinal cord are probably feebly depressed. It is probable that the alkaloid does not directly act upon the circulatory apparatus except to paralyze the pneumogastrics.

**Therapeutics.**—The paralytic action of conium naturally suggests its use in spasmodic affections; and accordingly it has been tried in *chorea*, in *paralysis agitans*, in *whooping-cough*, and in other diseases of similar nature. As the depressant influence of conium is chiefly upon the motor nerve, and as the phrenic nerve seems more sensitive to its effect than other motor nerves, it is evident that the drug is very limited in its power for good. In *maniacal* and *hysterical excitement*, the drug in full doses is said to produce a highly favorable condition of calm and relaxation; and in the treatment of the insane, conium is much used by some alienists.

Conium was formerly employed to relieve pain or as a deobstruent and alterative in chronic glandular or arthritic diseases, and even in cancer, but for these purposes has passed entirely out of vogue. The belief that it possesses alterative qualities does not seem to be well founded.

**Toxicology.**—Full physiological doses of conium produce in man quietude, languor, and muscular weakness. After toxic doses the weakness becomes extreme, forcing the patient to the horizontal position, or causing him to stagger or fall from weakness of the legs when he attempts to walk. This weakness has in some cases been attended by burning in the mouth, fauces, or stomach, nausea, vomiting, and with a sense of pressure or even with severe frontal pain. As the case progresses the paralytic symptoms become everywhere pronounced. The pupils sooner or later dilate;\* amblyopia from paralysis of accommodation, diplopia from irregular weakness of the ocular muscles, and ptosis are almost universally present, and the voice may be weakened to a whisper or lost. Sensibility is maintained to the end. Free salivation or free sweating sometimes occurs.

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\* The experiments of Poehlmann (quoted by Husemann) show that very grave symptoms may be induced and yet the pupils remain natural; but sooner or later they probably always dilate.



The circulatory phenomena are very subordinate; though the pulse-rate may at first fall, later it becomes more rapid. Consciousness is usually preserved until the last, but may be lost in asphyxial coma some minutes before death, which results from paralysis of respiration.

After death from conium no distinctive lesions are to be found, only the usual indications of death from asphyxia. The treatment consists in the immediate evacuation of the stomach and the exhibition of tannic acid,—the tannate formed is, however, probably more or less poisonous,—with the use of external heat and of internal stimulants: artificial respiration should steadily be maintained so long as there is the faintest indication of cardiac action. No physiological antidote is known; but strychnine and other respiratory stimulants should be used.

We have met with accounts of but four fatal cases of such character.\* In one, that of the mistress of Dr. Hermann Jahn, from ten to fifteen drops of the alkaloid killed in a few minutes (quoted by Husemann).

In another case a medical electrician, suffering from blepharo-facial spasm, beginning four hours after the last of a previous series of divided doses of a fluid-extract amounting to one hundred and eighty drops, took at 4.10, 4.40, and 5.15 P.M. fifty minims (one hundred and fifty in all) of "Squibb's fluidextract." At 6.10 there were nausea, intense muscular weakness, partial ptosis, diplopia, and great difficulty of speech; the pulse was 60. Shortly after this the man became unable to speak or to swallow. He made signs for electricity, and, on being asked whether the chemical or the faradic current, indicated the latter, and also the place of application of the electrodes, but was unable to hold one of the latter. Shortly after this, on being raised up, he dropped dead. A fourth case, in which a child five years old died of asphyxia preceded by coma and paralysis as the result of taking a drachm of chloroform-water containing five grains of the extract of conium, is recorded.†

**ASPIDOSPERMA.**—*Quebracho.*—Aspidosperma is the bark of an evergreen South American tree, *Aspidosperma Quebracho-blanco*. It contains at least six alkaloids, *aspidospermine*, *aspidospermatine*, *aspidosamine*, *quebrachine*, *hypoquebrachine*, and *quebrachamine*. The aspidospermine of commerce (amorphous aspidospermine) is not a pure principle, but probably contains all the alkaloids of the bark. According to Merck & Co., it consists principally of aspidosamine.

**Physiological Action.**—The general physiological action of aspidosperma has not been carefully enough studied to permit definite conclusions concerning its effects. It would seem that the various alkaloids have entirely different effects upon the system and in some respects are even antagonistic; thus, Schiffer has found that the extract of quebracho-blanco causes in the rabbit general muscular weakness with greatly diminished reflexes and increased frequency in breathing. Eloy and Huchard found that aspidospermine, quebrachine, and hypoquebrachine produced violent convulsions, which were followed, when the dose was large, by paralysis. According to Penzoldt, aspidospermine produces complete motor paralysis in the frog, with slowing of the pulse.

**Respiration.**—Penzoldt was the first to describe the marked action of quebracho upon the respiration. He described the effect produced in a dog as dyspnoea. In an elaborate research by Wood, Jr., and Hoyt on the effects of the commercial aspidospermine, it was shown that this substance produces a marked increase in both rate and depth of the respiration, the amount of air moved being augmented

\* See *Edinburgh Med. and Surg. Journ.*, 1845; *Sanitarian*, June, 1875; *P. J. and Tr.*, xvi, 102.

† According to H. Hayashi and K. Muto, the minimum fatal dose of coniine for rabbits intravenously given, is between fifteen and twenty milligrammes.

in some cases four hundred per cent. Secondary depressions was produced only by doses large enough to kill, and in these cases the stage of diminished respiratory activity was very short.

H. C. Wood, Jr., has since found (research not yet published) intense congestion and ecchymoses in the lungs following the intravenous injection of quebrachine.

**Blood.**—Penzoldt noted that the blood in the veins as well as in the arteries after the administration of aspidosperma had a bright red hue, and attributed the increase in the respiration to a dyspnoea brought about through the inability of the corpuscles to give up their oxygen. Wood, Jr., and Hoyt, however, believe that the change in the blood is the effect rather than the cause of the increased breathing. They were unable to find any spectroscopic change in the blood, either in the poisoned animal or when the aspidospermine was added to the blood outside of the body; they were unable to note any diminution of the oxidation power of the aspidospermine blood towards guaiac, and finally they noted that if the animal was asphyxiated the blood assumed the venous hue all over the body.

**Circulation.**—According to Wood and Hoyt, commercial aspidospermine produces a marked temporary fall of the blood-pressure, which was permanent if the dose had been large. During the period of low blood-pressure, it was found that irritation of the central end of the vagus produced a rise of pressure, showing that the vaso-motor system was not paralyzed. As the pulse was not slowed, it would seem probable that aspidospermine lowers the blood-pressure by a depressant action on the cardiac muscle.

**Temperature.**—Penzoldt found that, although quebracho had but little effect on the temperature of the normal animal, in a dog with septic fever it caused marked diminution in the temperature. In clinical experiments, however, it did not seem to exercise such effect in human fevers.

**Therapeutics.**—Aspidosperma has been used with asserted good results in various forms of respiratory embarrassment, as *asthma*, *emphysema*, and *bronchitis*. It is even stated that it will relieve *uremic* and *cardiac dyspnoea*.

The commercial amorphous aspidospermine may be given as representing probably the whole effects of the drug, in doses of from one-eighth to one-half grain (0.008–0.03 Gm.); the dose of the fluidextract is a quarter to one fluidrachm (1–4 C.c.); of the solid extract, one to three grains (0.06–0.2 Gm.).

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## ORDER II.—CARDIANTS.

### FAMILY I.—CARDIAC STIMULANTS.

THE term cardiac stimulants is here used to designate a number of medicines which, when given internally, increase the power and force of the circulation, and are used by the physician for such purposes. There are some substances which are heart-stimulants in reality, but which possess other properties in so great a degree as to overshadow their cardiac relations, and are therefore not used by the physician to affect the circulation. Such medicines are considered in connection with those powers which give them their clinical value, and are not included in the present class. Some of the members of the present class are slow in their operation, some rapid. Some produce increase in the pulse-rate, some lower it. It is evident, then, that no general indications can be laid down for their use, but that medicines so diverse must be studied individually.

#### AMMONIUM.

Ammonia is a colorless, irrespirable, highly irritant gas, of a strong alkaline reaction, extremely soluble in water. It is obtained upon a large scale as a waste product in the manufacture of coal-gas, and is official in watery and alcoholic solutions and in various salts.

When ammonia gas is dissolved in water it unites, according to the generally accepted theory, with the elements of water to form the hydroxide of a base, ammonium, similar in its chemical properties to sodium and potassium. Thus  $\text{NH}_3 + \text{H}_2\text{O} = \text{NH}_4\text{OH}$ .

This base ammonium possesses marked physiological properties, and eight of its salts are official. In many of these salts, however, the acid radical is so much more important than the basic that they are considered in the articles on their acid constituents. In this article is considered only the action of the ammonium base and those salts in which the acid radical is of little importance.

*Ammonium hydroxide* is known only in the form of its solution. This is colorless, with the characteristic pungent odor of ammonia and an alkaline taste. The concentrated solution is actively caustic.

*Ammonium carbonate* of the U. S. Pharmacopœia is a mixture of the acid ammonium carbonate and ammonium carbamate and should yield 31.58 per cent. of gaseous ammonia. It has an alkaline reaction and the characteristic odor and taste of ammonia. It occurs in white, translucent, fibrous masses, which on exposure

become opaque and efflorescent, parting with both ammonia and carbonic acid. It is soluble in four and a half times its weight of water.

*Ammonium chloride* or Sal Ammoniac, when pure, is a white crystalline powder freely soluble in water, *without odor*, but having a pungent salty taste. It is neutral or slightly acid to litmus.

#### Official Preparations:

Aqua Ammoniae Fortior (28 per cent.).....	Not used internally.
Aqua Ammoniae (10 per cent.).....	15 to 45 minims (1-3 C.c.).
Spiritus Ammoniae (10 per cent.).....	15 to 45 minims (1-3 C.c.).
Spiritus Ammoniae Aromaticus.....	15 to 45 minims (1-3 C.c.).
Ammonii Carbonas.....	5 to 10 grains (0.3-0.6 Gm.).
Ammonii Chloridum [Sal Ammoniac].....	5 to 10 grains (0.3-0.6 Gm.).
Linimentum Ammoniae (35 per cent.).....	External use.

*Local Action and Elimination.*—In solution, ammonia is a very powerful irritant and even escharotic, producing, if kept in contact with the skin, blistering, and finally sloughing, and causing the most serious disturbances of mucous membranes which it reaches. This local action is sufficient to interfere with its absorption, and it is difficult to produce distinct constitutional symptoms with it in man. Its volatility and the extreme fugaciousness of its action would seem to indicate its elimination by the lungs; but Feltz and Ritter were not able to find it in the breath of poisoned animals, and Magnus has apparently demonstrated that it will not pass through the alveolar walls. Bence Jones believed that ammonia is oxidized in the system because he found that its administration increases the acidity of the urine and also the amount of nitric acid. The theory that some portion of the ammonium is, in conjunction with carbonic acid, converted into urea is held by many physiologists.\* The neutral salts of ammonium are mostly eliminated unchanged (see Rabuteau).

*Physiological Action.*—When ammonium hydroxide is injected into the veins of animals in considerable quantities, it causes violent convulsions, with remarkable disturbances of the respiration, followed, if the dose has been large enough, by death in a very short time. Billroth states that the temperature falls enormously in animals poisoned with ammonia.

*Cerebrum and Spinal Cord.*—Ammonium has no effect upon the cerebrum. The tetanus produced by it in the lower animals is accompanied by great increase of the reflex activity (Funke), and is certainly of spinal origin, since it occurs below a section of the spinal cord (Lange, Formanek) and is not prevented by tying the artery of a limb (Funke). It would therefore appear that the toxic dose of ammonium is a powerful stimulant to the motor spinal cord. Upon the sensory cord it seems to have little or no action.

*Respiration.*—The intravenous injection of ammonia causes in the animal a great acceleration of the breathing, which after large doses

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\* This theory is of such purely physiological interest that it is dismissed with the following key to the literature: *Arch. f. Exper. Path. u. Pharm.*, ii., viii., x. 125, xii. 77; *Zeitschr. f. Physiolog. Chem.*, ii. 29, iv. 36; *Zeitschr. f. Biol.*, xiv.

may be preceded by temporary arrest of respiration in expiration. The cause of this arrest is uncertain, Funke observing it after section of the vagi, while in the experiments of Lange it was always absent. Section of the vagi, however, does not interfere with the increased rapidity of the breathing, the change from the deep breathing of divided vagi to the extremely rapid respiration of ammonia-poisoning being colossal (Funke). Further, Binz has found that the increase of the respiratory rate in chloralized rabbits is accompanied by a great increase in the amount of air breathed. Ammonium is, therefore, a powerful direct stimulant to the respiratory centres.

*Circulation.*—The intravenous injection of ammonium hydroxide both in normal and curarized animals produces an immediate fall in the blood-pressure, followed by a very decided rise if the dose has not been too large. If, on the other hand, an overwhelming amount of ammonium or one of its salts is employed, the fall of blood-pressure continues until the arrest of the heart in diastole. When the dose has been sufficient, this cardiac arrest is immediate. In the experiments of Lange and of Formanek, the primary fall of blood-pressure occurred after section of the spinal cord, also after ligation of the aorta; without doubt it is due to the direct action of the concentrated drug upon the heart. The rise of pressure which is the characteristic effect of the moderate dose of ammonium must be due to a stimulating action upon the heart or upon the peripheral vessels, since, according to both Lange and Formanek, it occurs after previous section of the cord. The experiments of Formanek, in which it was shown that if the thoracic aorta were temporarily ligated, ammonium still distinctly elevated the blood-pressure, demonstrate that the drug acts upon the heart directly, but it is probable that the muscle-fibres of the arterioles are also affected; so that the conclusion must be reached that ammonium is a primary stimulant both to the heart and to the muscle-fibres of the arterioles, although when in overdose it is a paralyzant to both heart and arterioles.

In regard to the action of ammonium upon the pulse-rate, the evidence is somewhat discordant. All observers seem to be in accord that the pulse is for a time increased in rate, which increase in rate, according to Lange, does not occur after section of the spinal cord, and according to Formanek, is prevented by extirpation of the stellate ganglion of the sympathetic. The increased rate appears, therefore, to be due to a stimulating influence upon the cardiac accelerators. Formanek has found that at the time of the highest pressure there is marked slowing of the pulse, which is prevented by section of the vagi, and which he concludes, therefore, to be due to stimulated inhibition.\*

According to F. W. Böcker the long use of ammonium chloride is accompanied by a decided decrease in the solids of the blood,—an observation confirmed by Arnold.

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\* Formanek believes that the vagi are directly stimulated, but his tabulated experiments seem to show that the reduction of the pulse-rate is inconstant, and it is possible that it is a secondary result due to high blood-pressure.



According to Feltz and Ritter, the blood of a dog killed by ammonia is incapable of absorbing oxygen, and contains much less than the normal amount of gas, while the red disks resist the action of acetic acid to a markedly abnormal degree.

**Therapeutics.**—Externally, ammonium hydroxide is much used as a constituent of irritating liniments, and, on account of its efficiency and cheapness, is very valuable. By inverting a watch-glass full of the stronger water of ammonia upon the skin, a blister may be raised in a very few minutes; but, as the effects of the application are apt to be severe, the use of it is justifiable only under rare circumstances.

Internally, ammonium is largely used for the relief of acute heart failure, as in *shock* and *collapse*. It must be remembered, however, that the drug is not well absorbed through the gastric mucous membrane and if used, therefore, as a circulatory stimulant, it should be administered hypodermically; or better, intravenously. In failure of the heart from anesthetics\* or other poisons, animal or vegetable, in *sudden collapse* in disease, as is sometimes seen in the *exanthemata*, in *cholera*, and not rarely in *pernicious malarial fever*† or after *surgical operations* or *injuries*, hypodermic injections of ammonia have seemed to be in a number of reported cases of very great service. The effects seen in fainting by holding various forms of ammonium below the nostrils, usually in the form of smelling salts, is due to a reflex stimulation the result of irritation of the nasal mucous membrane. The ammonium being an irrespirable gas it is evident that sufficient of it cannot be absorbed to exercise any direct action upon the circulation. Moreover, similar results may be obtained by tickling the nose with a feather. When the failure of the circulation depends upon a slow and persistent cause, as in *adynamic fevers*, ammonia is not generally useful, but may be employed as an adjuvant to alcohol in the crisis of the disorder. As a stimulant, ammonia may be useful in poisoning by *venomous serpents*, but the statements that have been made that it is antidotal to venom have no foundation. (For detailed discussion, see the tenth edition of this treatise.)

Ammonia appears to have a tendency to act upon the mucous membrane of the lungs, and its salts, especially the carbonate and the chloride, are used as stimulant expectorants in *acute bronchitis* when free secretion has just been established. In *chronic bronchitis* it may be administered from time to time when the secretion is not very free.

Although there is sufficient reason for believing that ammonium chloride especially affects the respiratory mucous membrane, the statement of Böcker, that it hastens very greatly the nutritive changes and the exfoliation of the epithelium in all mucous membranes, is in accord with clinical experience as to its value in various gastro-

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\* Ringer (*Practitioner*, xxvii.) finds that ammonia added to the frog's heart depressed with chloroform, iodoform, etc., has a pronounced effect in re-establishing its action.

† See Zuelzer (*Revue de Thérap. Méd.-Chir.*, July 1, 1872).

intestinal conditions. In Germany more than in this country it has been extensively used in the treatment of *chronic gastric* and *intestinal catarrhs*. The statement of W. Stewart, made in 1870, that it is an effective remedy in *chronic torpor of the liver* and *chronic hepatitis*, has been sustained by subsequent clinical experience, and it has become a standard remedy in these affections and in *catarrhal jaundice*. The dose in hepatic diseases is twenty to thirty grains (1.3–2 Gm.) in four or five ounces of water, three or four times a day, administered when the stomach is empty. As a stimulant antacid, it is frequently of service in cases of *headache from gastric acidity*. (See p. 632.)

**Toxicology.**—Ingested in large amount, ammonia acts as a violent corrosive poison, the symptoms of its constitutional action being entirely lost in those caused by its local influence. Violent pain in the mouth and fauces, in some cases intense burning in the larynx with sense of choking and great difficulty of breathing and rapid asphyxia; more commonly violent abdominal pain, vomiting, bloody purging, and other symptoms of gastro-enteritis, mark its escharotic effects. Death from œdema of the larynx may occur within five minutes. More usually the fatal result is wrought out more slowly, with collapse and sometimes convulsions secondary upon the local effects. In some cases symptoms of impending suffocation, resulting in death from asphyxia, have occurred, and at the autopsy intense redness and congestion of the bronchial mucous membrane have been present, due no doubt to the irritant's having found its way into the bronchi. The intellect may be clear to the very moment of death, or stupor, and finally coma may be developed. If the victim survive for a few hours, recovery usually occurs, but the convalescence is commonly protracted, and permanent ill-health may result from the destructive lesions produced by the poison. These lesions are to be found not only in the respiratory and gastro-intestinal tracts, but also in the kidneys.

The neutral salts of ammonium being only slightly irritant are much less actively toxic. Oesterlen affirms that he has seen two ounces of the chloride taken by man without the production of more serious results than violent gastro-intestinal pain and diarrhœa, while older observers state that two drachms of the salt are sufficient to cause death in a dog. According to Arnold, thirty grains will kill a rabbit in ten minutes; but Rabuteau found that one drachm injected intravenously produced in the dog only vomiting, muscular weakness, temporary paralysis of the hind legs, and general prostration, lasting four or five hours. When given for a length of time in very large doses it affects the general nutrition. We have seen extreme prostration and a typhoid condition apparently produced by the taking of half an ounce per diem for some days, while great prostration, with an eruption of bloody blebs, hematuria, and hemorrhages from the mucous membranes, has been reported by Isham as caused by the continuous use of the drug.

The treatment of poisoning by ammonia consists in the neutralization of the ammonia as soon as possible by vinegar or other dilute acid, and the meeting of indications as they arise. If the œdema of the glottis be threatening, tracheotomy should at once be performed.

**Administration.**—As stated above, when ammonium is used as a circulatory stimulant it should be given hypodermically. For hypodermic use a water of ammonia or a solution of the ammonium carbonate is to be preferred.

### CAMPHOR.

Camphor is a stearopten which is obtained in China, Japan and the neighboring islands by boiling the comminuted wood of the root of the *Cinnamomum Camphora*, a handsome evergreen tree which sometimes reaches a height of fifty or sixty feet. The camphor which arises to the surface of the boiling water is skimmed off and partially purified by sublimation—coming into commerce as *crude camphor*, which occurs in grains of a whitish or pinkish color—and is finally purified by sublimation with lime.\*

Refined camphor (or, as it is commonly called, *camphor*) occurs in disks or hemispherical bowl-like translucent masses, of a fibrous or granular fracture. Its taste is hot and peculiar; its odor very strong and characteristic; it is volatile, inflammable, tough, but readily pulverized on the addition of a few drops of alcohol; melts at 347° F.; is soluble in one thousand parts of cold water,† in one part of strong alcohol, and still more soluble in chloroform; thrown upon water, a granule of camphor floats, and exhibits a rotatory movement.

#### Official Preparations :

Camphora .....	5 to 15 grains (0.3–1.0 Gm.).
Aqua Camphoræ (0.8 per cent.) .....	$\frac{1}{2}$ to 2 fluidounces (15–60 C.c.).
Spiritus Camphoræ (10 per cent.) .....	15 to 30 minims (1–2 C.c.).
Camphora Monobromata .....	5 to 10 grains (0.3–0.6 Gm.).
Linimentum Camphoræ (Camphor 1 part, Cotton Seed Oil 4 parts) .....	External use.
Ceratum Camphoræ (10 per cent.) .....	External use.
Linimentum Saponis (4.5 per cent.) .....	External use.

**Local Action, Absorption, and Elimination.**—Camphor, though primarily a local irritant and stimulant, probably has a narcotic action on nerve-endings in the mucous membrane, in this way relieving intestinal spasm. It is slowly absorbed and in great part or altogether oxidized in the organism, probably changed first into camphorol, and being excreted in the urine as campho-glycuronic acid, and amido-glycuronic acid (Schmiedeberg and Meyer).

**Physiological Action.**—The ordinary dose of camphor (five to fifteen grains) produces when taken internally a feeling of warmth in the stomach, with in some cases a sense of slight exhilaration and quietness, and some, but usually not a pronounced, acceleration of

\* Borneo camphor, yielded by the *Dryobalanops Camphora*, is very highly valued in the East, but does not reach this country. Stockman has found that both it and the *Ngai camphor* of China act on the organism like camphor. See Pellicani. A number of other camphors, such as *Camphor-Cymol*, *Bornylamin*, *Amido-Camphor*, *Campherol*, have been examined by various investigators, and found to resemble true camphor very closely in their physiological action.

† By rubbing the camphor up with magnesia in water, the latter can be made to take up much more than one part in one thousand.



the pulse. In doses of from twenty to thirty grains it causes lassitude, giddiness, lessening of the pulse-rate, preceded in some cases by a brief period of excitement.

Upon the lower forms of life camphor acts as a very feeble germicide; to the articulate it is a violent poison; in the frog it produces stupor with primary paralysis; in birds, according to Menghini, it causes stupor or delirium, with epileptiform seizures; and in mammals vomiting, violent convulsions, coma, and death, apparently from asphyxia, follow its ingestion.

*Nervous System.*—The precise action of camphor on the nervous system is not clearly understood. In the lower animals when given in a large dose it causes convulsions followed by paralysis. The convulsions are of cerebral origin. Upon the spinal cord the drug seems to act primarily as a mild stimulant and secondarily as a depressant.

The convulsions which are caused by the toxic dose are certainly of cerebral origin, since C. Weidemann, Hoffmann (quoted by Weidemann), and Gottlieb have shown that they do not spread to the lower segment of the body after section of the cord; and R. Stockman has found that in the rabbit they do not occur after removal of the cerebral cortex. That the toxic dose finally produces cerebral paralysis is shown by the coma which is so frequent a symptom of camphor-poisoning.

In the frog the regular course of paralytic symptoms produced by camphor are, first, loss of voluntary movement, the reflexes being intact; second, loss of reflexes, the muscles still responding when the motor nerves are stimulated; third, loss of function in the motor nerves, the muscles responding still to direct stimuli. It is probable that the loss of the power of voluntary movements is due to paralysis of the psycho-motor centres, although it may be the outcome of some interruption of the power of the cord to carry impulses from these centres to the motor cells in the cord.

According to the experiments of Binz, Grisar, and Gottlieb, small doses of camphor increase reflex activity by a direct action upon the motor side of the spinal cord, but the experiments of Stockman appear to have yielded a different result, so that there is uncertainty in the matter.

The toxic dose of camphor depresses the spinal cord, and, as was first shown by Weidemann, later the motor nerve-trunk, beginning with their peripheral endings.

*Muscles.*—Upon the muscles themselves camphor exerts a very feeble influence. Locally applied to the muscles in the form of solution or vapor, a notable effect is produced, but in general poisoning this is not evident. In experiments of Cesare Rossi, made with a Mosso's ergograph, camphor given internally seemed to distinctly increase the energy and endurance of the human muscle, but in other cases it entirely failed to manifest any such power; so that if it have any direct action as a muscle stimulant, such action must be feeble and uncertain.

According to the experiments of Meyer, the absence of convulsions in camphor-poisoning in the frog cannot be explained by paralysis of the spinal cord or motor nerves, since before these conditions are developed the brain is profoundly affected; nor does the local application of camphor to the brain in the frog produce convulsions. Meyer believes, with probable correctness, that the absence of convulsions is due to the rudimentary development of the cerebral system in the frog.

*Respiration.*—According to Stockman and Binz, camphor increases the rate of respiration greatly; and Lewin found that the amount of respired air moved was markedly increased in the rabbit by it.

It would appear, therefore, that the moderate dose of camphor is a respiratory stimulant, and as there is probably some stimulation of the cord by the drug, the inference is that such stimulation is due to an action upon the respiratory centres. The asphyxia of advancing camphor-poisoning indicates that the respiratory centres finally share with the other motor centres of the spinal cord the paralyzing influence of the overwhelming dose of the drug.

*Circulation.*—Although clinical experience seems to indicate that camphor has a profound effect upon the circulation, our knowledge of its action is incomplete and uncertain. It has been directly shown by the concurrent experimental results of Heubner and Harnack and Wittkowski, Weidemann, Umpfenbach, Maki, and Stockman that the drug decreases the rate and increases the energy of the contractions of the isolated frog's heart,\* and it may be considered established that upon the frog's heart camphor acts as a stimulant.

On the other hand the evidences of stimulation of the heart in mammals is far from satisfactory. At times camphor, when injected in small doses directly into the circulation of a mammal, increases the arterial pressure, but this increase is never constant or persistent and is often absent, the characteristic effect of the camphor being depression of the arterial pressure. It is of course possible for a drug to stimulate the heart, and yet so widen the blood-path as to produce no increase in the arterial pressure; but although Gottlieb and Maki and Lewin believe that they have obtained evidence of cardiac stimulation, other observers have failed to do so. It probably, however, is a stimulant to the cardiac muscles and widens the blood-vessels, partly by an action on the vaso-motor centres and partly by a direct influence on the arterial walls.

The statement of Heubner, that camphor will re-excite the movements of the frog's heart when arrested by muscarin, has been abundantly confirmed. Harnack and Wittkowski found that the atropine increases the contraction-rate of the camphorized heart, that stimulation neither of the vagus nor of the sinus is able to arrest cardiac contraction, and that muscle paralyzants like the soluble copper salts and apomorphine do stop the heart's beating.† Böhme found that camphor is capable of causing the heart arrested by chloral to recommence beating. The question whether the drug acts upon the muscle or upon the ganglia is still unanswered, and certain actions of camphor upon the frog's heart are not easily explained. Thus, in Maki's experiments with Williams's apparatus, some minutes after the application of the camphor the blood-pressure fell below the norm, to rise very shortly under very powerful pulsations of the heart. Then the blood-pressure would sink, to rise again in a little while, and again to sink. This alternation would occur several times. These experiments of Maki have apparently not been confirmed, but are especially interesting in relation with the periodic rise and fall of blood-pressure which has been noted in mammals by Weidemann and others.

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\* The contrary results of Alex. Lewin were probably due to the use of overwhelming doses, in such doses camphor certainly being a cardiac depressant.

† In repeating Harnack and Wittkowski's experiments Stockman failed to get satisfactory results.

Stockman reached the conclusion that camphor depresses the vaso-motor centres and probably produces a vascular dilatation which masks the increased action of the heart,—a conclusion which is in accord with the statements of both Maki and Lewin, that in chloralized animals, when the vaso-motor centres are deeply paralyzed, camphor elevates the pressure; but in Lewin's experiments, when the action of the chloral was profound, the pressure failed to rise under the influence of the camphor; and H. Winterberg determined that camphor does not raise the arterial pressure when chloral is given sufficiently to certainly paralyze the vaso-motor centres. Further, all attempts to demonstrate the stimulating action of camphor upon the more or less isolated heart of the mammal have so far yielded contradictory results. Gottlieb obtained an apparent stimulating influence from the camphor, but Winterberg, using the method of Langendorff for cardiac isolation, failed entirely, except in two experiments, to get any evidence whatever of cardiac stimulation. Seligman, although showing in some cases stimulation, was unable to demonstrate any constant influence on the normal mammalian heart, but found that camphor was capable of restoring coordinate beats to a heart thrown into fibrillary contraction.\*

As is shown by Weidemann, during the convulsive stage of camphor-poisoning there is a marked rise of the arterial pressure, which, however, may be prevented in great measure by curarization and artificial respiration, and is therefore evidently chiefly due to the convulsions and disturbances of breathing. In the curarized animal Weidemann found that camphor caused remarkable periodic alternating elevation and fall of the arterial pressure, which are prevented by section either of the cord or vagi, but whose nature Weidemann did not determine. Stockman found that, at least with Borneo camphor, such action is extremely inconstant, and Winterberg has demonstrated that when the curarization is complete the oscillatory phenomena are absent, so that they are probably due to obscure spasmodic movements.

*Sexual Function.*—Camphor has been largely praised by some medical practitioners as a sexual stimulant, by others as a sexual depressant. Almost invariably, however, it has been administered in combination with other more potent drugs, to which any apparent influence of the remedy has probably been due. There is certainly no experimental and apparently no sufficient clinical reason for believing that camphor acts more decidedly upon the sexual centres of the spinal cord than it does upon other nerve-cells of the same region.

**SUMMARY.**—Camphor causes convulsions through its effect upon the brain; the therapeutic dose probably has a quieting influence on the cerebral cortex. In large doses it acts as a depressant to the motor cord, while the small doses are probably stimulant. It is a stimulant to the respiratory centres, and probably to the cardiac muscle, but does not greatly raise the blood-pressure on account of its widening the blood-vessels, probably both peripherally and centrally.

**Therapeutics.**—Camphor is very frequently given internally as an antispasmodic, to quiet restlessness and "*nervousness*." It is also employed in certain painful affections seen in those persons who are especially liable to the condition of the nervous system just men-

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\* Rosenstein, in his research, concluded that camphor has a stimulating influence upon the heart, though a very fleeting one. With borneol, Pellicani obtained fall or periodical oscillations of pressure. Lewin was only able to obtain a fall of the arterial pressure, and Gottlieb reached the conclusion that probably camphor increases the capability of the heart to respond to stimuli, so that, while the normal systole is not altered, in pathological condition there is such an increased excitability that the heart is capable of great efforts.



tioned: thus, it is often useful in *nervous headaches* and *dysmenorrhæa*. Indeed, in the latter disease, either alone or combined with opium in bad cases, it is a most valuable drug, but must be given freely. In *diarrhæa* not dependent upon inflammation, in *nervous diarrhæa*, in *cholera*, and even to some extent in *cholera*, camphor is an efficient remedy, allaying intestinal pain and spasm, and also checking intestinal secretion. It enters into a large proportion of the popular cholera-mixtures. In sudden *cardiac failure* and in *adynamic conditions* it has been largely used, especially in Germany; but while it probably has distinct value when given hypodermically, it ought not to be relied upon to the exclusion of more potent drugs. According to Schilling, thirty grains a day may be given hypodermically in the profound adynamia of acute *endocarditis*, *typhoid fever*, *pneumonia*, etc., with the happiest result. In our experience its action in these states has been, though prompt and marked, but a transient one. The use of large doses of camphor in *abnormal sexual excitement*, and in *chordee*, has about passed out of vogue, which also is true of its employment in severe convulsive disorders such as *whooping-cough*, *epilepsy*, and *puerperal convulsions*. In *hysterical convulsions*, as in other phenomena of similar origin, camphor is a useful antispasmodic.

Externally, camphor is much used in liniments as a stimulant application for *bruises*, *sprains*, etc.

**Toxicology.**—After poisonous doses of camphor the symptoms, which are tolerably uniform, are as follows: faintness, headache, vertigo, confusion of ideas, burning pain in the stomach, dyspnoea, delirium, spasms deepening into violent convulsions, coma, with complete insensibility and absence of all reflexes; the pulse, at first full and quick, later becomes small and sometimes slow; the skin is cool, pale or livid, generally bedewed with sweat. Glycosuria has been noted by Stockman. Sudden unconsciousness, with or without convulsions, has been in some instances the first manifestation of the action of the poison, and in any individual case many of the symptoms detailed above may be wanting. Although camphor has in many cases produced very alarming symptoms, over two hundred grains of it have been taken without permanent result, and the recorded fatal poisonings are very few. The only ones known to us are—adult, quantity unknown; sickly infant, ten grains; child two years old, unknown amount; fatal abortion produced by three drachms.\*

**Administration.**—Large doses (ten to fifteen grains) of camphor are best administered in emulsion, because when given in this way, being very finely subdivided, they create as little irritation as possible, and are rapidly absorbed; smaller doses may be given in pill. For hypodermic use a ten-per-cent. solution in olive oil should be preferred. As an antispasmodic, the Camphor Water is usually preferred.

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\* Cases, *Edinburgh Med. Journal*, May, 1873; *The Clinic*, March, 1873; *Wiener Medizinische Presse*, 1874, 258; *Berlin. Klin. Wochens.*, Sept. 1873-74; *Trans. Lond. Clin. Soc.*, 1874, 27; *London Lancet*, 1876, ii. 71; *British Med. Journ.*, Feb. 1875; 1877, i. 607; Sept. 1895; June, 1896; *St. Petersburg Med. Wochens.*, 1897, xiv.; *Austral. M. J.*, June, 1888; *N. Y. M. R.*, March, 1887.

The *Oil of Camphor* occurs in our market as a reddish or yellowish-brown liquid, having a strong odor of camphor, and a hot, camphoraceous taste. It contains camphor in solution, and is probably equivalent to it in physiological action, except that it is locally more stimulating, and preferable in intestinal disorders. Dose, five to ten minims (0.3–0.6 C.c.).

CAMPHORIC ACID (*Acidum Camphoricum*) is produced by boiling camphor with concentrated nitric acid. It occurs in small white, acicular or scaly crystals, free from odor, of a feebly acid taste, sparingly soluble in cold, freely in hot, water, also in alcohol, ether, and fatty oils. It was originally proposed by Fürbringer as an antiseptic of practical value for the disinfection of the intestinal canal, and in the treatment of *tuberculosis* and ammoniacal *cystitis*: as first noticed by Wittkowski it is a very valuable antihydrotic in the *night-sweats* of *phthisis*; how it acts in these cases has not been determined. Max Reichert, Niesel, and other physicians have found it very serviceable as a local application in the treatment of tubercular and other *catarrhs* of the upper and lower air-passages.

According to Fujitani, sodium camphorate acts as a depressant to the motor side of the spinal cord and is also stimulant to the heart. The evidence he presents of the last fact, however, is not convincing. Bohland asserts that camphoric acid is rapidly eliminated, the whole of a single dose escaping from the kidneys in the course of five hours unaltered. In *cystitis*, fifteen grains (1 Gm.) may be given three or four times a day; for *night-sweats*, fifteen to thirty grains may be administered at bedtime, or, when the sweat occurs late in the night, the dose may be divided, the patient being awakened to take the last dose after midnight. Gastric irritation and even vomiting have been noted after thirty grains, and Niesel saw severe renal irritation in a patient who had taken in four weeks fifty grammes.

*Oxycamphor*.—This oxidation product of camphor is a white, crystalline powder, soluble to two per cent. in cold water; is alleged to have a calmative action upon the respiratory centres while strengthening the cardiac muscle and the central and peripheral vaso-motor nervous system. It has been used with asserted excellent results in *dyspnœa* from cardiac weakness, and from tubercular and other chronic diseases of the lungs. Dose, eight to fifteen grains (0.5 to 1 Gm.)

## ALCOHOL.

Absolute Alcohol,—*i.e.*, ethyl alcohol containing not more than one per cent. by weight of water,—is a colorless, volatile liquid, boiling at 172° F., not congealed by a cold of –166° F., and having the specific gravity of 0.797. It is used only for chemical purposes. Alcohol of the Pharmacopœia contains 94.9 per cent., by volume, of absolute ethyl alcohol, and has the specific gravity of 0.816; Diluted Alcohol contains 48.9 per cent., by volume, of absolute ethyl alcohol.

Alcohol also exists in Whisky and Brandy, which are obtained respectively by the distillation of fermented grain and of fermented grapes, and should contain from forty-five to fifty-five per cent. of absolute alcohol, and in the official *Red Wine* and *White Wine*. For medicinal use, brandy should be at least four and whisky two years old.

### Official Preparations :

Alcohol (95 per cent.).

Alcohol Absolutum (99 per cent.).

Alcohol Dilutum (49 per cent.).

Spiritus Frumenti [Whisky] (44 to 55 per cent.).

Spiritus Vini Gallici [Brandy] (44 to 55 per cent.).

Vinum Album.

Vinum Rubrum.

*Local Action.*—Alcohol is an active irritant, but is not corrosive. It is also a pronounced germicide, which when in proper concentration is capable of killing all protoplasms.

According to the researches of C. Harrington and H. Walker, against dry bacteria absolute alcohol and ordinary commercial alcohol are wholly devoid of bactericidal power, while forty-per-cent. alcohol is effective within five minutes against most non-sporulating pathogenic bacteria. In order to destroy some of the strongly resisting bacteria, whether dry or moist, sixty- to seventy-per-cent. alcohol is necessary. Preparations of alcohol more concentrated than seventy per cent. do not, however, act more powerfully upon bacteria than do the weaker preparations, so that for the practical disinfection of a wound sixty- to seventy-per-cent. alcohol should be preferred; the contact should be maintained for at least five minutes.

*Absorption and Elimination.*—Alcohol is absorbed with great rapidity by the stomach, but, as has been shown by Von Mering, is also hurried on into the intestines. It is without doubt taken up freely into the whole length of the alimentary tract. In Baum's experiments symptoms of intoxication appeared in a horse fifteen minutes after its injection into the rectum. (For a study of the point of elimination in the system, see page 198.)

*Physiological Action.*—*Nervous System.*—We have not met with a close experimental study of the order in which the nervous centres are affected, but it is scarcely doubtful that alcohol acts upon them as does ether, except that the latter substance, being much more volatile than alcohol, is consequently absorbed and eliminated much more rapidly, so that its influence is more evanescent. We know by experiment that the vapor of alcohol is capable of producing the stupor known as anesthesia, and, further, that this anesthesia may be deepened into death, accompanied by all the phenomena of fatal ether-narcosis. There has been, in the past, much discussion as to whether the small dose of alcohol had a stimulant action on the intellectual centres. Without going into details, in our opinion, there seems to be no satisfactory evidence that alcohol in any dose is a true cerebral stimulant. The increased garrulity of the alcoholic is due to a paralysis of the will rather than a stimulation of the mind. The observation of Dogiel, that in the alcoholized dog both sensory and motor nerves are markedly depressed, without doubt holds good for acute alcoholism in man. Whether this depression is due directly to the alcohol or to the changes produced by it is uncertain. It cannot be denied that the continuous effect of large doses of alcohol upon the nervous tissue is depressant.

The original experiments of Heinrich Dehio, showing that changes can be demonstrated in the ganglionic cells of the brain in animals killed by the large dose of alcohol, have been repeated and extended by Colin C. Stewart with corroborative results.

*Circulation.*—The action of alcohol upon the circulation has been the subject of a great deal of investigation and dispute. Much of the evidence is so contradictory that positive conclusions are very difficult. We believe, however, that from the mass of investigation it



may be fairly deduced, that in moderate doses alcohol has a slight stimulant influence upon the cardiac muscle, and at the same time it produces a dilatation of the blood-vessels of the skin; these actions may so counter-balance each other that there is little or no change in the blood-pressure, although there is evidence that in many cases alcohol may produce a slight rise of pressure. After exhibition of large doses, the drug acts as a depressant to the heart and also widens the vessels, probably through direct influence as well as an effect upon the vaso-motor centres.

Much of the evidence concerning the physiological action of alcohol is entirely useless on account of the size of the doses which were applied. Although a number of experimenters have failed to obtain a rise of blood-pressure from any dose of alcohol, yet various investigators, as Dogiel, Castillo, Kochmann, Eagleton, Bachen and Dixon, have all noted more or less marked elevation of the pressure from the injection of alcohol. According to Dixon the failure to obtain rise of pressure by many observers has been due to the action of the anesthetic which was employed. In the experiments of H. C. Wood and D. M. Hoyt, although in the majority of cases alcohol failed to produce rise of pressure, in certain instances there was a distinct elevation of the blood-pressure. Those who have investigated the question are almost unanimous that, after section of the spinal cord, there is a distinct rise of pressure. This fact, which was originally noted by Castillo, has been confirmed by Abel and by Wood and Hoyt, and would point very strongly to the increase in the cardiac activity.

Studies have been made upon the isolated frog's heart by Umpfenbach (1881), by Ringer and Sainsbury (1883), by Maki (1884), and by Dresser (1888), with the general conclusion that alcohol is a direct depressant to the cardiac muscle; while Castillo (1880), Eagleton and Cerna have reached opposite conclusions; so that the present experimental evidence on the subject is contradictory so far as the isolated frog's heart is concerned. According to Wood and Hoyt most of this evidence is unavailable because of the lack of delicacy of the methods employed, and in their experiments they obtained, uniformly, evidence of stimulation of the frog's heart. Martin, Hemmeter, and Kochmann in experiments upon the isolated mammalian heart were unable to observe any evidence of increased work. Upon the other hand, Bachen, Loeb, Dixon and Bachmann, all obtained evidence of the increased action of the warm-blooded heart under the influence of alcohol. According to Bachmann and to Dixon, this stimulation is similar to that which is caused by the addition of glucose to Ringer's fluid and they believe that it is a result of food upon the heart-muscle. The theory that the blood-pressure is not affected by alcohol, despite the stimulation of the heart, on account of the widening of the vessels, is further borne out by the observations of Hemmeter and by Wood and Hoyt—that alcohol increases the velocity at which the blood flows through the vessels, and by the sphygmographic experiments of Wood and Hoyt.

The studies of the effect of alcohol upon the circulation of the human being are mostly lacking in sufficient accuracy to make them of scientific value; but Cabot and Binz in sphygmomanometric observations fail to discover any rise of blood-pressure. On the other hand Kochmann, with doses of from five to ten C.c. of absolute alcohol, obtained uniformly a distinct rise in the blood-pressure; larger quantities than this produced a greater or lesser fall, according to the dose.

*Blood.*—There seems to be little reason for supposing that alcohol in therapeutic dose has an appreciable effect upon the blood, but as long ago as 1841 C. H. Schulz observed that mixed with the blood outside of the body it not only causes coagulation, but also separation of the hemoglobin from the corpuscles. It is probable that to the action of the alcohol upon the hemoglobin is due the fact noted by

Schmiedeberg that alcohol mixed with blood lessens its ability to yield oxygen in the presence of a reducing agent. Jaillet and Hayem state that in rapid alcoholic-poisoning in animals extensive alteration in the blood-corpuscles can be discovered, many of these bodies being shrivelled and altered in form, with yellow precipitates of hemoglobin in their interior.

*Temperature.*—Owing no doubt to the sensations of warmth induced by its local action on the stomach and by the increased activity of the circulation in the extremities, alcohol was formerly looked upon as a promoter of animal heat. This view was questioned as early as 1848 by Duméril and Demarquay, and has been studied and written about to an enormous extent. The matter has been so thoroughly worked out that it does not seem wise to do more here than give results, and to refer the reader who is desirous of following up the literature of this subject to the tenth edition of this treatise.

In the lower animals small doses of alcohol produce a slight increase of the bodily temperature, which rarely in mammals reaches more than  $1^{\circ}$  F. Larger doses of alcohol produce a fall of temperature in the animal proportionate to the size of the dose. According to Ruge, when the dose has not been sufficient to cause distinct intoxication, the fall usually amounts to from  $\frac{1}{3}^{\circ}$  C. to  $\frac{2}{3}^{\circ}$  C., rarely reaching one degree. When there is distinct narcosis the fall may amount to  $3^{\circ}$  C., or with a lethal dose to  $5^{\circ}$  C. Bouvier and other observers have found that the effects of large doses of alcohol are even more marked in animals suffering from pyemic fever; the reduction of temperature may amount to  $8.5^{\circ}$  C., and the fever be altogether put aside by the narcotic dose. The effect of alcohol upon the temperature in man is parallel to that which is produced in the lower animals; the fall from large doses is, however, less pronounced, probably because the cerebrum of man is proportionately much more sensitive to alcohol than is that of the animal, and narcosis results from smaller doses of the poison. Again, in persons accustomed to the use of alcohol the elevation of the temperature does not appear; and, indeed, it cannot always be produced in a normal subject. Further, the habitual use of alcoholic stimulants greatly lessens the depressing influence of alcohol upon the bodily temperature, so that the temperature of the drunken man is not always below the normal. As, however, intoxication becomes more profound the tendency to a fall of temperature is more and more marked.

The fall of temperature produced by alcohol is largely due to an excessive loss of heat, but the relations of alcohol to thermogenesis form such an integral portion of its action on nutrition that its discussion will be postponed to that heading.

*Respiration.*—According to the experiments of Binz, of Fonteyne and of A. Jaquet, small doses of alcohol increase the number and amplitude of the respiratory movements. The toxic dose of alcohol decreases the respiratory air movement. The drift of the present

evidence is to show that the action is centric, and that alcohol stimulates or paralyzes the respiratory centres according as it is in small or large amount.

Jaquet certainly failed to prove the truth of his conclusion that the increase of respiratory movement produced by alcohol is due to local irritation; and in a later research Binz, by means of controlled experiments, apparently demonstrated the incorrectness of Jaquet's theory. Binz has extended his experiments not only to the lower animals, but also to man, in whom he found that the increase of the respiration is distinct although not very large, and is much more pronounced in those who have been previously fatigued.

*Nutrition.*—The question of the effect of alcohol upon the nutrition divides itself naturally into two sub-questions: Its direct drug-action upon the chemical processes of the body, and its possible food value as an oxidizable hydrocarbon.

In regard to the first point, as the result of a vast amount of experimentation, much of which is contradictory, it appears that the only fair conclusion is that alcohol has very little if any direct action upon the heat production, or the elimination of carbonic acid or nitrogenous waste products.

In regard to the possible food value of alcohol, it may be considered to-day as proven that a small dose of alcohol, corresponding to about three ounces of absolute alcohol, is practically entirely oxidized in the system, only about one to five per cent. escaping consumption. Second, that the result of this burning up of alcohol is the production of energy which may be utilized to a certain extent by the economy, and lessen the oxidation of the bodily tissues; or, if looked at from another point of view, diminish the amount of hydrocarbon food necessary to maintain nutritive equilibrium. To this extent, therefore, alcohol must be regarded as a food, that is, as a substance which the system is capable of oxidizing for the production of useful energy. On the other hand, it would seem established that alcohol is not capable of being stored up as a reserve food, that is, not only can it not enter into the composition of the proteid tissues of the body, but unlike fatty foods and the starches, it cannot add to the amount of fat in the system, except indirectly by offering a more easily oxidizable substance and thus preventing the burning up of the other hydrocarbon elements of the food.

The attempts to determine the action of alcohol on metabolism by studying heat formation have failed to produce any evidence of a positive effect.

The first calorimetrical studies upon alcohol were those by Bevan Lewis. He found that in the rabbit alcohol sometimes produces a primary lessening of heat-production, most marked and pronounced after small doses, followed by a marked increase in heat-production, most pronounced after large doses of the alcohol. In five observations by E. T. Reichert and H. C. Wood upon dogs, the average results were in accord with those by Bevan Lewis, although their individual experiments yielded somewhat varying results. In some of these experiments heat-dissipation more than kept pace with the increase of heat-production, and the bodily temperature fell. In other instances the bodily temperature rose, showing that heat-production was increased more than heat-dissipation. In a further series of experiments



E. T. Reichert obtained, in five experiments, increased heat-production, and in thirteen decreased heat-production, the difference not depending upon dose, and the range of variation of result being as much as sixty-five per cent., a strong indication that there was something wrong with the method or the experiments.

These results are somewhat discordant and varying, but certainly indicate that alcohol has no such immediate dominating influence upon tissue change as greatly to increase heat-production. The fall of bodily temperature which occurs after toxic doses of the drug is without doubt due to an excessive heat-dissipation, which in turn is the result of vaso-motor paralysis, and the mere excessive loss of heat has a profound influence in provoking increased heat-production just as increased heat-production has a profound influence in inducing increased heat-dissipation; so that much care is necessary in the consideration of calorimetical studies of large doses of vaso-motor paralyzants. But if the action of alcohol were pronounced it should manifest itself over all indirect and disturbing influences. On the whole, therefore, the earlier calorimetical studies indicate that alcohol does not pronouncedly and directly affect those nutritive processes through which the animal heat is maintained, a conclusion which is confirmed in the very elaborate memoir of Atwater and Benedict, who, using small doses of alcohol, found that in man the increased heat-production was no greater than could be accounted for by the potential energy of the alcohol oxidized.

The effect of alcohol upon the elimination of carbonic acid by the lungs has been investigated by several observers, with different results.

According to the researches of Böcker, of N. S. Davis, of Hammond, of Perrin, of Boeck and Bauer, of Rumpf, and of Bodländer, there is a lessening in the amount of carbonic acid gas exhaled. On the other hand Henrique, Wolfers and Zuntz obtained evidence of increased carbonic acid elimination; E. Smith found that small doses of alcohol increased the elimination of the gas, although brandy, whisky, and gin always lessened the production.

If alcohol really did have a direct powerful influence upon oxidation in the general system the conclusions of investigators should be more in accord, and it would seem, therefore, improbable that alcohol has any marked action on the carbonaceous metabolism.

The determination of the action of the drug upon the chemical movements of protoplasm, and the destruction of albuminous materials in the body, is of course to be made by a study of its effect on the nitrogenous elimination.

The studies on the elimination of nitrogenous waste products, made by Riess, Keller, Munk, Norris and Smith, and Rosenfeld indicate—despite the contrary results obtained by Donogány and Tibald—that alcohol diminishes slightly the quantity of urea excreted. This effect is, however, no more than might be expected from the addition of an oxidizable hydrocarbon food to the dietary. In Rosenfeld's experiments nitrogenous equilibrium having been produced in a man, alcohol was given with the result that the amount of nitrogen eliminated was markedly decreased; after this period sugar was substituted for alcohol, and the eliminated nitrogen still remained lower than the intake. During the alcohol period the amount of uric acid eliminated was distinctly above the normal; during the sugar period this was not the case. Rosenfeld concludes that since uric acid arises generally from the nucleated albumin, the alcohol has spared the nuclein-free proteid tissues at the expense of the nucleo-albumins. According to Beebe, when alcohol is taken in conjunction with purin-free diet, the proportion of the uric acid in the urine is not augmented, but when the diet contains this type of food-stuff the uric acid excretion is increased. He interprets these results to mean that the drug interferes with the function of the liver to prevent the complete oxidation of nuclein foods to urea.

Beebe's results have, however, been contradicted by Jackson and Blackfane, who find that, even on a diet free from all nitrogenous foods, the elimination of uric acid is increased, the urea and total nitrogen remaining unaffected.

In studying the question of the possible food value the first thing is to determine whether alcohol is oxidized in the system. This

question has been investigated by Baudot, Schulinus, Lieben, Anstie, Thudichum, Subbotin, Edes, Bodländer, and Strassmann, with concordant results. After moderate doses of alcohol from one to two per cent. can be recovered from the urine and about an equal quantity in the breath, and, as no aldehyde or other alcohol derivative can be found in the body, it must be concluded that from ninety-five to ninety-eight per cent. is completely oxidized into carbonic acid and water.

A. Benedicenti finds that an increase in the amount of ingested alcohol does not greatly influence the elimination through the lungs, but that lowered temperature markedly lessens such elimination. Abelous, Bardier and Ribaut found that when alcohol is given in from one to three C.c. per kilo in the warm-blooded animals from eighty-seven to ninety per cent. of it is destroyed within eight hours. In the frog ninety per cent. of the alcohol injected could be recovered from the body under four days; after seven days, however, none remained in the system. Finally, W. O. Atwater and F. G. Benedict, as the result of elaborate studies made upon human beings in a respiratory chamber, found that when an amount of alcohol corresponding to six ounces of whisky was taken, the average elimination was one and nine-tenths per cent.

A further confirmation of the theory that asserts the oxidation of alcohol in the body is found in the experiments of H. Ford, which, if accurate, demonstrate that alcohol is formed in the body out of hepatic sugar.

Working on a very large scale, by the distillation of the blood of animals, Ford obtained in weighable quantities a substance which he believed to be alcohol.\* Further, Ford distilled various tissues, also blood from the lungs and liver. He also made elaborate calculations, based on the carbon ingested and on the carbon exhaled, as to the amount of alcohol which ought to be found in the capillary blood of the lungs, and found experimentally quantities corresponding to his calculations. He found that the smallest quantity of alcohol is to be obtained from fresh liver-tissue, and the greatest from putrescent liver-tissue, in which the glycogen must have undergone fermentation.

These researches of Ford are corroborated by the discovery, first made, we believe, by A. Lieben, although usually attributed to Dupré, that a substance exactly resembling alcohol exists in very minute quantity in the urine even of teetotalers.† M. Béchamp, apparently without a knowledge of the work of the other chemists, obtained, from the urine of persons who had not taken any alcoholic beverage for a long time, alcohol in sufficient quantity to burn it. As Lieben also found that this substance exists in the urine of dogs, horses, and lions, and as A. Rajewski obtained it from healthy rabbits, and as further, Hoppe-Seyler (quoted by Bowditch and Hodge) states, "traces of alcohol are found in human organisms such as the brain, muscles, liver, not only after alcoholic indulgence but without this they seem to be constantly present," it appears to have been proven that alcohol is found in the normal human organism, and probably subserves some need of the processes of the body.‡

If alcohol be oxidized in the body, it must of course generate force, measurable by the modern standard of the heat-unit. A little calculation will show the impor-

\* Space is wanting to describe in detail the very elaborate methods employed by Ford. The tests which he relied on, to prove that the liquid obtained was alcohol, were the chromic acid test, the peculiar inflammability, and the optical appearance of the alcohol in the conducting-tubes at the time the distillate commenced to boil.

† It has been asserted that the substance "is not alcohol. It passes over among the earliest products of distillation, yields acetic acid on being oxidized, reduces the potassium dichromate when dilute sulphuric acid is present, and its aqueous solution has a lower density than water. It furnishes iodoform, and exists in the urine in a very small quantity." Possessing the physical and chemical characters of alcohol, to ordinary minds it is alcohol.

‡ Dörning and Praetorius found that fecal matter on decomposition yielded alcohol to such an extent as to suggest a possible remunerative source. Von Meyer and O. Mohr, working independently, found that the amount of alcohol in the fecal matter was too small for commercial product (*Chem. Centrbl.*, 1904, I. 636).

tance, or rather the great amount, of the generated force. According to Dupré, one gramme of alcohol oxidized in the body evolves 7184 units of heat, while the same weight of lean beef gives off only 1482 units of heat. It has been estimated that 9.3 ounces of lean beef—equal to about two ounces of alcohol—will supply the necessary force to maintain the circulation and respiration of an average man for one day. That is, four ounces of strong spirit will suffice for this purpose.

The ergographic studies made by Lombard, Kraepelin, Scheffer, and other investigators, afford no proof that alcohol in moderate dose has a direct action upon the working power of the muscle. An underlying, almost unsurmountable difficulty in this method of experimentation is the impossibility of separating the indirect from the direct effects of alcohol. The experiments which have been made with the isolated frog's muscle indicate that alcohol has, when in appropriate dose, a direct stimulant effect either upon the intra-muscular nerve-endings or the sarcolemma. Further, when there is a lack of sufficient food, alcohol seems to be especially useful for the purpose of increasing muscular power and probably is used by the muscle as power-source. Large doses of alcohol depress the muscle; apparently its action upon voluntary muscle is very similar to its influence upon the heart-muscle.

Lombard Warren found that small doses of alcohol increased, larger doses diminished, his muscular power. Dastre found that alcohol first temporarily increased, afterwards depressed, the muscle, so that the whole muscular work done when under its influence was less than normal. In H. Frey's studies the alcohol lessened the working power of the normal muscle, but markedly refreshed the nearly exhausted muscle, a refreshment which Frey believes to be due to the alcohol supplying an oxidizable material to the muscle which had exhausted its stored-up force-producing material. Scheffer reached the conclusion that alcohol at first increases the muscular working power and shortly afterwards diminishes it. Schnyder determined that alcohol in small quantities, taken by the individual when tired and in a fasting condition, exerts a favorable influence upon the force of the muscles; an influence, however, which is less than that of ordinary food of equal caloric value; also, further, that when there is an abundance of food, alcohol fails to make itself manifest; and in any case if in large amount, by its action upon the nervous system depresses muscular force. F. S. Lee and W. Salant found that dilute alcohol, about forty parts by weight to one thousand of the frog, quickened both contraction and relaxation, delayed fatigue, and increased the amount of work possible to the isolated muscle.

These considerations warrant the statement that in a *certain sense alcohol is a food*,—i.e., *that it is capable of being used for the purpose of the organism*; but it does not necessarily follow from this that alcohol is capable of replacing fats and hydrocarbons in food. In attempting the determination of this, two methods have been used,—that of Von Noorden and that of Atwater.

According to the *Method of Von Noorden* the individual is brought into a condition of nitrogenous equilibrium by careful feeding, and when this condition has been thoroughly established, non-nitrogenous articles of food are withdrawn and alcohol substituted in isodynamic quantity. Under such circumstances, if the alcohol be superior to the hydrocarbon in replacing the nitrogenous material, less nitrogen should be eliminated than before its administration; if the power of the alcohol be less than that of the hydrocarbon, more nitrogen would be thrown off; if the alcohol just replaced the hydrocarbon, the nitrogenous equilibrium would not be disturbed.

Stammreich's experiments upon himself were two in number. In the first experiment there was a distinct lessening of the elimination of nitrogen during the alcohol period, showing that the alcohol replaced the nitrogenous material more actively than the corresponding fat mass for which it had been substituted. In the



second experiment, with a lessened amount of nitrogen in the food, there was at first no pronounced change in the nitrogenous elimination, followed, however, after two days by a marked increase, which continued for three days after the withdrawal of the alcohol. A third set of experiments were made with very little nitrogen in the food. Under these circumstances there was a great increase of the elimination of nitrogen during the alcohol period.

As the result of the comparison of various experiments Von Noorden reached the conclusion that when the food is rich in albuminous compounds, alcohol is able to replace hydrocarbon or fats; but when the food is poor in albumin, it cannot do so. A similar series of experiments have been made by K. Miura. In the experiments—in which food with but little nitrogen was given—the results obtained by Miura were similar to those of Stammreich. On the other hand, in opposition to Stammreich, Miura found that when the food is rich in albuminous material, alcohol is not able to replace the non-nitrogenous foods. Miura believes that these differences depend in part upon the facts that in Stammreich's experiments the alcohol was substituted for fats, while in his experiments it replaced carbohydrates, which, according to Voit, have greater power of sparing the nitrogen materials than have the fats; so that alcohol might be equivalent to fats and yet not to carbohydrates. Neumann, after producing in himself nitrogenous equilibrium, omitted half of the fat from his diet, causing thereby nitrogenous loss. By substituting alcohol for the fat he found that there was a return to nitrogenous equilibrium. In a subsequent period, after re-establishment of nitrogenous equilibrium, he added alcohol in doses increasing up to one hundred grammes a day, with pronounced nitrogenous gain. In a third period, the alcohol was continued, but a part of the fat was withdrawn, which caused a slight nitrogenous balance. From these experiments Neumann concludes that alcohol has the property of sparing the proteids, but is probably not capable of entirely replacing the fats.

In the extraordinarily elaborate research made by W. O. Atwater and F. G. Benedict,\* three selected men were kept for periods varying from five to nine days in a respiration calorimeter, in such a way that the heat-production and all the excretions from the body, liquid and solid, could be studied. On some days no exercise was taken; on others by means of a stationary bicycle, a large amount of measured work was done. The diet was regulated with scientific accuracy. On the alcoholic day one gramme per kilogramme of bodily weight of alcohol was taken in six doses; a quantity of alcohol which seems small but whose potential energy was about one-fifth of the total diet energy in the rest-period, and one-seventh of the total diet energy in the work-period. It was determined in these experiments that the potential energy of the alcohol was transformed by the body into kinetic energy as completely as was that of the ordinary nutrients; also that the efficiency of alcohol in the protection of body-fat was equal to that of the corresponding non-alcoholic diet; alcohol, isodynamic amounts of fats and other carbohydrates having, therefore, equal protective power against loss of fat. The efficiency of the alcohol in protecting the protein of the body was evident but usually not entirely equal to that of isodynamic amounts of ordinary nutrients, although in some of the experiments alcohol seemed to protect protein equally with ordinary food.

In regard to muscular work, the experiments seem to show that the total energy of the ordinary diet is utilized a little more thoroughly than is that of alcohol, but the difference was so small as to be entirely within the limits of experimental error; it was, on the average, less than one per cent. of total energy, and is, therefore, of very little importance.

It is proven that alcohol when taken in moderate amount is oxidized in the body, and in this process of oxidation it must yield

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\* The research of Atwater and Benedict deserves much more thorough discussion than can be given in the text of this book. It seems to us most remarkable in conception and execution, and for the present at least these results ought to be taken as conclusive. The method employed in its directness is in our thinking far more likely to yield the truth than is the indirect plan of producing nitrogenous equilibrium. The number and extent of the experiments also are out of comparison with those of the early workers.

kinetic or active energy. The researches which have just been epitomized seem to us to definitely determine that this kinetic or active energy is employed by the organism for life purposes, and that alcohol *must be considered as a food capable to some extent of replacing hydrocarbons*. It must be remembered in applying this scientific knowledge, however, that the organism can only consume a limited amount of alcohol, and that, therefore, the food value of alcohol has narrow limitations.

*Digestion.*—It is definitely proven that alcohol when in small amount outside of the body does not markedly affect the activity of the digestive ferments, yet, in the living animal, by provoking secretion, by increasing peristaltic activity, or in other ways it may really stimulate natural digestion. In larger quantities—more than ten per cent.—it markedly inhibits the digestive power of the ferments. The alcoholic beverages influence digestion through some other principle than the alcohol contained, for it has been shown that the malt liquors lessen the activity of peptenzyme out of all proportion to their alcoholic content, and that the wines are also more harmful to digestion than a corresponding amount of pure alcohol.

The laboratory researches of W. Buchner, of R. H. Chittenden and L. B. Mendel, and of William Roberts are concordant and conclusive. The results reached are as follows: Salivary digestion is not very actively affected by the presence of pure alcohol; indeed, when there is not more than four or five per cent. the digestive power of ptyalin seems to be increased: ten per cent. of absolute alcohol (*i.e.*, twenty per cent. of proof-spirit) retards it slowly. On the other hand, wines and malt liquors very greatly hamper salivary digestion almost in exact proportion to their degree of acidity. Pure alcohol seems to increase rather than diminish gastric-juice digestion until the amount rises to two or three per cent.; less than ten per cent. appears not to be constantly and demonstrably inhibitive; after twenty per cent. the digestive action may be reduced to one-third. A very important fact is that the retardation produced by a given percentage of alcohol varies greatly with the activity of the ferment and the nature of the material to be digested. Chittenden and Mendel have found that three per cent. of alcohol distinctly retards the proteolytic action of the pancreatic juice, while, according to A. Dastre, fifteen per cent. puts an end to the artificial pancreatic digestion of nitrogenous materials.

Chittenden, Mendel, and Jackson found that alcohol temporarily increases the flow of saliva reflexly by its irritant influence upon the mucous membranes of the mouth; and that it increases the secretion of gastric juice very greatly, the action on the stomach being exerted not only by alcoholic fluids in the stomach but by absorbed alcohol. They further determined that the ordinary alcoholic drinks agree in stimulating gastric secretion, and that the gastric juice secreted was stronger in hydrochloric acid and in proteolytic power than normal. It is worthy of note that in experiments made by Chittenden upon healthy dogs with gastric fistulas, using proteid test-meals, digestion was never retarded nor accelerated, leading to the conclusion that in those cases there was a practical balance between the two antagonistic actions of alcohol upon the digestion.

Radzikowski experimentally determined that when alcohol is taken into the stomach in small amount it increases the secretion of gastric juice, and also its contained acid and pepsin. In confirmation of this, Spiro found that an enema of from seven to ten C.c. of alcohol causes in man a free secretion of a very acid gastric juice in the empty stomach, an effect which is probably due to an excretion of alcohol into the stomach, since M. N. Grehant has proven that when alcohol is injected into the blood it is excreted into the stomach. Storck finds that the

digestion of starch within the mouth is increased by the local action of preparations of alcohol of the strength of from two to five per cent., but delayed by stronger preparations.

**SUMMARY.**—Alcohol in large amount is a depressant to the cerebral and spinal ganglionic cells, as well as the nerve-trunks. The action of small doses upon the respiratory centres is not thoroughly established, but is probably stimulant; large doses depress the respiratory centres, and finally may cause death by centric paralytic asphyxia. Upon the heart the small dose of alcohol acts as a direct stimulant, the large dose as a depressant or paralyzant. The influence of minute doses upon the vaso-motor system is not thoroughly worked out, but there appears to be a widening of the blood-paths at a time when the heart is still stimulated, so that there is a marked quickening of the blood-movement. The toxic dose of alcohol paralyzes the blood-vessels, probably both centrally and peripherally. The peripheral temperature is often increased by small amounts of alcohol, and there may be even a slight increase in the central temperature, probably caused by quickening of the circulation; the large dose of alcohol lowers the animal temperature, probably by causing vaso-motor paralysis, and thereby increasing heat-dissipation.

Alcohol has no specific influence upon the production of heat or of carbonic acid, or upon nitrogenous elimination, and, therefore, it has little or no direct effect upon the nutrition, unless it be in poisonous doses, when it certainly disturbs all nutritive processes. After absorption into the blood, alcohol is to a limited extent eliminated through the lungs, the skin, and the kidneys unchanged, but is largely, and when in small amount practically wholly, burnt up in the system. In its destruction it yields kinetic energy which is employed by the organism for its purposes so that it (alcohol) is capable to a considerable extent of replacing the hydrocarbons of ordinary food, and must be considered to have definite food value.

**Therapeutics.**—Our knowledge of the physiological properties of alcohol shows that its chief therapeutic value in acute disease is as a stimulant, a temporary imparter of power which will enable the system to stand some strain of short duration,—to bridge over some period of weakness.

The cases to which it is especially adapted may be divided into three classes:

*First.*—Those in which there is a temporary loss of heart-power, as in fainting from exhaustion, loss of blood, or other cause. In these cases the alcoholic stimulant should, if possible, be given hot, and not much diluted; with it should also be exhibited some more rapidly acting diffusible stimulant, such as ammonia.

*Second.*—Those acute diseases in which the powers of the system are in danger of being used up; to aid in the digestion of food and in the maintenance of power. Alcohol, as has already been stated, is to a certain extent a food, but it will not of itself sustain life for a long time, and should in adynamic disease always, unless for special reasons, be combined with milk, or occasionally with eggs. One great



source of its value in these diseases is the power it imparts of assimilating food, and in milk punch are furnished the stimulant to digestion and the most perfect food known for digestion. This use of alcohol is apart from its office in the lowest stage of fever as a heart- and nerve-stimulant. Employed for this purpose it is useful in *all* stages of the *adynamic fevers*, such as *typhus* and *typhoid*.<sup>\*</sup> By the exhibition of three or four ounces of milk every two hours, with one or two drachms of brandy or whisky, from the beginning of the attack, in many cases the development of the severe adynamic symptoms may be prevented.

A. Ott claims to have experimentally determined upon a fever patient that the value of alcohol as an albumin-saving food is equal to its isodynamic equivalent of a pure food hydrocarbon.

In the advanced stages of *pneumonia*, *pyemia*, *exanthematous fever*, and other acute diseases, when the typhoid state is well developed, alcohol should be given boldly, to quiet by stimulation the nervous and circulatory systems, to afford a food which will in a measure replace the natural pabulum, to aid in the digestion of milk and other simple nourishment, to aid in lowering temperature: in a word, to enable the system to stand the drain upon its vital powers, and at the same time to check such drain.

Although a great deal of work has been done upon the subject, the question as to whether alcohol does or does not, when given in moderate dose, increase the resisting power of the system to infectious diseases cannot be at present answered with positiveness.

Binz found that alcohol increases the resistive power of the dog to septic material, but his experiments seem to have been too few to be of value. In an incomplete research, H. A. Hare and M. E. Pennington found that alcohol increases the bactericidal property of the blood at least against some pathogenic organisms. Gruber affirms, as the result of experimentation, that the frequent administration of small doses of alcohol to guinea-pigs, infected with bacillus prodigiosus, prolonged life, and in some instances even brought about restoration. Opposed to these results are those of various investigators. Doyen and Thomas both found that alcohol increases the liability of animals to infection with cholera. Abbott, using streptococcus pyogenes, bacillus coli, or staphylococcus pyogenes aureus, found that the alcoholized animals died with much more certainty than did those of the control experiments in which no alcohol was given. Deléarde reached the result that alcohol destroys the immunization of rabbits against tetanus and anthrax. Laitinen, in a very elaborate research upon three hundred and forty-two animals, representing six species of mammals and birds, using anthrax, tubercle bacilli, and diphtheria toxin, arrived at the conclusion that alcohol diminishes very distinctly the resistance of the body towards infectious diseases. Pawlowsky found that alcoholized animals reacted much more freely to staphylococcus citreus than did the normal animal. Gruber and Koegler determined that alcoholization increases the mortality of animals infected with the pneumobacillus. Goldberg came to a similar conclusion in regard to the influence of anthrax on pigeons. Ausems found that the administration of alcohol in small doses to rabbits before infection diminished their resistance.

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<sup>\*</sup> The statement of J. H. Kellogg (*Journ. Amer. Med. Assoc.*, 1895, xxv.), that the administration of brandy markedly lessens the toxicity of the urine in typhoid fever, suggests a very important line of research.

At first sight the experimental evidence which has just been epitomized would seem sufficient to determine that alcohol diminishes rather than increases the power of the system to resist various infections, and also puts aside immunization. Undoubtedly, however, as clearly pointed out by S. J. Meltzer, the doses of alcohol which have been used by experimenters have been toxic and not therapeutic, so that the importance of the researches is largely invalidated. Moreover, in most cases the alcohol has been given through the stomach-tube, with, as insisted upon by Abbott, resulting erosion and gastric inflammation distinctly complicating the bodily condition of the animal.

Properly administered, alcohol always promotes, not arrests, secretion in fever cases. The guide to the amount given should be the effects produced; so long as the drug lowers temperature and pulse-rate, moistens the dry tongue and skin, and quiets the nervous disturbance, it does good; if, however, the tongue grows dryer, the pulse puts on an angry, bounding character, and the patient becomes restless and uneasy, stimulation is being pushed too far, and the amount exhibited should be lessened. Whenever the *odor of liquor appears upon the breath*, the patient is almost certainly *taking too much*.

The antipyretic action of alcohol has suggested its use in cases of high temperature; as, however, this is only one of its actions, and is not decided unless very large doses be given, alcohol cannot be employed as a general febrifuge. True arterial excitement and sthenic inflammation certainly contraindicate its use. The rule may be laid down as follows: high temperature is an indication for the use of alcohol only when other symptoms also demand it; in itself high temperature is never a contraindication to alcohol. In *acute sthenic diseases*, after the progressive stage has passed and the results of the disease simply remain to be overcome, alcohol and milk will often save life. Thus, in *acute pneumonia*, when so much consolidation has occurred as to render it doubtful whether the exuded matter can be removed, or in *abscess*, when large amounts of pus have formed, the demand may be urgent for alcohol as a food and as an aider of digestion, and sometimes as a stimulant.

*Third.*—Those cases in which there is a depressing agent present. In many forms of *poisoning* alcohol may be used with signal advantage simply as an arterial and nervous stimulant, to overcome the influence of a depressing agent. Thus, when death is threatened from cardiac failure in poisoning by *toxines*, *venom*, *aconite*, or similarly acting toxic agents, whether of animal or of vegetable origin, alcohol is an important remedy, unless the poison, as in the case of an anesthetic, is physiologically so closely allied to alcohol that the small dose of alcohol becomes a reinforcing depressant. In acute depression threatening a fatal issue it should be administered freely, not much diluted, and, if convenient, hot. From one to four fluid-ounces of whisky should be given, repeated every ten or fifteen minutes, until slight intoxication, convalescence, or death has resulted.

What has been said up to this point in regard to the therapeutic action of alcohol has had reference to acute disease. The value of the drug in some chronic diseases cannot be doubted; but in prescribing it the physician should never lose sight of the possible danger of producing a habit far worse in its fruits than is death itself.

In *chronic neuralgia*, in *hypochondriasis*, and in *melancholia*, temporary relief may sometimes be obtained by the use of stimulants; but the very relief afforded doubles the temptation to the frequent use of the alcohol, and, as the system becomes habituated to its action and the dose has to be more and more increased, the habit of frequent stimulation grows almost of necessity into drunkenness. For this reason we do not think that the physician is ever justified in prescribing alcohol for its narcotic stimulant effect in these cases. The chief legitimate uses of alcohol in chronic diseases are to aid in digestion, to furnish a food which, without any digestive effort upon the part of the system, shall be absorbed, and shall take the place of more ordinary food, and to check excessive tissue-waste. Of course these indications exist only in such diseases as are either dependent upon, or closely associated with, a condition of the system in which the general nutrition is depraved. In purely local affections the use of alcohol is rarely called for except in the last moments of life, when it may always be employed to afford relief and to protract for a short time the struggle. In *chronic dyspepsia*, alcohol administered with the food often aids very materially in the assimilation of the latter; but care should be exercised in prescribing it, for the same reasons as were given a moment since when speaking of the use of stimulants in *melancholia*. In many cases of *chronic neuralgia*, not as a narcotic stimulant, but as a food and a stimulant to nutrition, alcohol is often of service. The danger of establishing a fatal habit in this disease is, however, excessive. In almost all cases in which alcohol is called for in *neuralgia*, cod-liver oil is also indicated, and it is generally best to exhibit the two remedies together, so as to obtain the easy assimilation of the oil and to guard against evil moral results.

In *phthisis*, and its congener *scrofulosis*, while there is room for doubt it is probable that the use of alcohol may often prove beneficial; and in the latter stages of consumption its judicious use as an antipyretic narcotic stimulant to lessen the sufferings of the patient is perfectly justifiable. During the earlier chronic movements of the affection, alcohol taken with cod-liver oil, or in small amounts with the food at meal-times, conduces not so much to the comfort as to the well-being and recovery of the patient.

The experience of Arctic explorers has clearly shown that alcohol has no heat-producing power, so that at a time when it was believed by physiologists to have such influence the Northern navigators had learned that the free use of spirits, far from enabling a man to withstand habitual exposure to intense cold, very materially lessened his power of resistance. On the other hand, the experience of almost every trout-fisherman has satisfied him that spirits do have power



to prevent "catching cold" under sudden and unaccustomed exposure to wet and cold, and that benumbed extremities will become warm and have their proper feelings return under the influence of a glass of whisky. There is, however, nothing strange or contradictory in these experiences, and they are both in strict accord with our present knowledge of the physiological action of the drug. As is often the case, the facts were practically made out, however, before science could solve the apparent paradox. It has been abundantly shown that alcohol has no heating power; but the chill of sudden exposure, the suffering benumbed extremities, the bronchitis that perhaps follows, all mean simply this: that, as a result of the cold, the blood leaves the surface and the extremities, the circulation fails in the outposts, and as a consequence, suppressed perspiration—*i.e.*, suspended function of the skin—and internal congestions follow. The relief afforded by the spirits, as well as the prevention of sickness, is due simply to the power of the remedy in maintaining the circulation and keeping the external surfaces warmed by the constantly renewed currents of fresh blood from the interior of the body.

As an *antiseptic* alcohol is sufficiently active to be useful on occasion as a dressing for wounds. Lint soaked and kept constantly wet with spirits may be applied.

**Administration.**—Almost enough has been already said upon this point, but a few further remarks seem appropriate. When stimulants are used to sustain the sinking powers in poisoning or in disease, the amount given should be almost solely regulated by the effects. Thus, in snake-bite it may be necessary to give a pint of whisky in the course of an hour; and in low fevers we have seen the greatest benefit result, and life apparently saved, by the exhibition of a quart of spirits a day. In snake-poisoning, one, two, three, or four ounces, as the case may seem to need, should be exhibited every ten minutes until some effect is produced or matters become hopeless. In low fevers half an ounce to an ounce should be given every one, two, or three hours, *pro re nata*, the practitioner watching the results.

The question of choice, of course, comes up in every case as to which of the spirits shall be used. We have never been able to perceive any distinct differences in their action (gin, of course, being excepted), save only that sometimes one spirit agrees better with the stomach than another. This has seemed to us to depend simply upon the personal likings of the patient, to which, therefore, the choice may well be left. In sudden collapse, some of the wines with a very high *bouquet* are believed to be more stimulating, on account of the ethers which they contain. In convalescence, and for habitual use in health, wines are preferable to spirits,—more agreeable, more tonic, and less likely to lead to excessive indulgence.

When a mild stimulant is wanted in the beginning of fevers, especially if milk punch seems too "heavy," *wine whey* may sometimes be used with advantage. It is made by pouring a half-pint

of sherry or madeira into a pint of boiling milk, stirring thoroughly, and, after coagulation has occurred, straining off the whey, which may or may not be sweetened, according to the taste of the patient. *Mulled wine* is often very grateful to patients as a change. It is made by beating an egg up thoroughly with three fluidounces of sherry and adding a like quantity of water, which must be actually boiling when poured in. *Champagne* is useful in patients with delicate stomachs, especially if nausea or vomiting actually exists, and also may be employed with advantage in sudden failure of the vital powers, especially in elderly persons. It must always be very "dry,"—i.e., as free as possible from sugar.

*Milk punch* is prepared by adding from a dessertspoonful to a fluidounce of brandy, whisky, or rum, according to the degree of stimulation required and the taste of the patient, to three fluidounces of milk, with sugar and nutmeg to taste. The addition of a tablespoonful of lime-water is not recognized by the palate, and renders the beverage more acceptable to the stomach when the latter is weak.

*Eggnog* is still more nutritious than milk punch, but is "heavier," and is usually rejected by the stomach if given too freely. It is made by beating up thoroughly the yolk of an egg with five fluidounces of milk and half a fluidounce to one fluidounce of spirits (and half a fluidounce of lime-water if required), and adding a sufficiency of sugar, with finally the white of the egg previously thoroughly beaten into a froth.

**Toxicology.**—The acute form of alcoholic poisoning in its minor degrees is, unfortunately, an hourly occurrence almost in every village, but that fatal results are not absolutely so rare as is generally believed is shown by the fact mentioned by Taylor, that in four years (1863–67) thirty-five deaths from this source occurred in England and Wales. It is worthy of note that in some fatal cases convulsions have preceded death.\* The absolute diagnosis of acute alcoholic poisoning when the patient is simply seen in the advanced stage of deep coma cannot be made out. The odor of liquor upon the breath or about the person is simply a proof that the subject has been drinking, not that the symptoms are caused by alcohol. The manifestations are merely those of profound compression or congestion of the brain, of apoplexy, of opium-poisoning; and a man whose breath and urine are loaded with alcohol may have been struck down with apoplexy or poisoned with opium. Whenever in drunkenness no answer is obtainable by shaking or hallooing at the subject, the existence of apoplexy should be strongly suspected, and a very careful examination made to detect facial or other palsy; even if this be not found, judgment should be suspended. As in apoplexy the bodily temperature is frequently elevated, while in acute alcoholism it is either normal or subnormal, the existence of fever would strongly indicate cerebral hemorrhage.

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\* See *P. M. T.*, vi. 463.

A congested ecchymotic condition of the mucous membrane of the stomach is the only lesion at all characteristic of an acute alcoholic poisoning.

The *treatment* is very similar to that of opium-poisoning except that in many instances care should be taken to maintain the bodily temperature. The stomach should be evacuated, the patient aroused by mechanical means, strychnine and digitalis given hypodermically, the hot bath employed if necessary, and, finally, if symptoms come to the extreme, long-continued artificial respiration (Sylvester or forced) should be practised. For the purpose of aiding in the elimination of alcohol large quantities of normal saline solution should be given by enemata, or preferably by hypodermoclysis. (For case, see F. C. Foster, *B. M. J.*, 1903, i.)

The results of chronic alcoholic poisoning, by their frequency and importance, have come practically to rank among diseases, and are discussed in treatises upon the practice of medicine, to which the reader is referred.

**METHYL ALCOHOL.**—*Pyroxylic Spirits. Wood Alcohol. Columbian Spirits.*—This is a mobile, colorless liquid, of a hot, pungent taste and aromatic odor, highly inflammable, mixing in all proportions with water, ethyl alcohol or ether. It is usually obtained by the destructive distillation of wood, and on account of its cheapness is largely used in the arts as a solvent.

Methyl alcohol is capable of producing an intoxication similar to that caused by ethyl alcohol, but distinct in the slowness of the onset and the extraordinary duration of the symptoms, which may last from three to four days after the comparatively moderate dose of the drug. After distinctly toxic doses the fall of the bodily temperature is very marked, and convulsive movements of rhythmic or choreic character, followed in a day or two by loss of sensation and reflex movements are common phenomena. Hemorrhage also frequently occurs from the abdominal tract. The eyes are especially affected, nystagmus of a pronounced type often being present, also dilatation of the pupil. Chronic methyl-alcohol poisoning is far more dangerous than is ordinary alcoholism, and amblyopia due to degenerative changes in the ganglion cells of the retina is a very common phenomenon. Both in human and experimental poisoning excessive fatty degeneration of the liver and other organs is usually found after death. Jelliffe reports multiple neuritis following the ingestion of methyl alcohol, and also after inhalation of the fumes.

*Methyl-alcohol amblyopia* may appear after a single debauch. It is accompanied with contraction of the fields, absolute, usually central, scotoma, and rapid failure of vision; and, though temporary improvement may occur, in ninety per cent. of the cases it ends in permanent loss of useful vision. It is worthy of note that in many cases methyl-alcohol amblyopia has resulted from the excessive use of essence of ginger or peppermint, or other aromatics, in which the alcohol has been used as a menstruum. It has also been caused by the absorption of the alcohol through the lungs and skin. It has been shown by A. Birch-Hirschfeld that the methyl-alcohol amblyopia is accompanied by demonstrable changes of the retinal nerve-cells, and also of the optic nerve.

The permanency and severity of the symptoms caused by methyl alcohol depend in part upon the slowness of its elimination, and in part upon the fact demonstrated by Reid Hunt,—that it is oxidized in the system with the formation of formic acid, a highly poisonous substance.

Methyl alcohol has been used to some extent in practical medicine, but appears to have no other remedial properties than those of ethyl alcohol, and to be a much more dangerous remedy. It has very properly fallen into complete desuetude as a medicine.



The treatment of methyl-alcohol poisoning is very unsatisfactory. The best that can be done is to aid in the elimination of the alcohol and of the products of its destruction within the body by free sweating and by the administration of large quantities of slightly alkalized water with sodium carbonate.\*

### CAFFEINE.

Caffeine is the active principle of a large number of plants which are used in various parts of the world for the purpose of making beverages. Originally discovered in the coffee bean (*Coffea arabica*), it is now manufactured commercially usually from tea leaves (*Thea sinensis*); it is also the active ingredient of the kola nut (from *Stereulia acuminata*); of maté (from *Ilex paraguensis*) of Yaupon or holly tea (from *Ilex cassine*) and of guarana (from *Paullinia cupana*). The last named is the only caffeinic plant recognized by the U. S. Pharmacopœia.

GUARANA is a dried paste, prepared from the seeds of *Paullinia cupana*, a Brazilian plant. It occurs in reddish-brown almost sausage-like masses, rugose on the surface, very hard, with an irregular fracture and a marbled appearance when broken. Its taste is astringent and bitterish; its odor somewhat resembles that of chocolate. The alkaloid *guaranine*, discovered in it by Martius has been shown to be identical with caffeine. The U. S. Pharmacopœia requires that guarana shall contain 3.5 per cent. of alkaloids. It has also in it free tannic acid and a fixed oil.

Caffeine occurs in long, snow-white, silky, opaque, odorless crystals, sometimes conjoined into feathery crystals, of a feeble bitter taste. It has a neutral reaction, but unites with acids to form salts. It is soluble, at 77° F., in 45.6 parts of water, 53.2 parts of alcohol, three hundred and seventy-five parts of ether, or eight parts of chloroform. It was first discovered in coffee by Runge, in 1820. In 1827 Oudry discovered a principle in tea which he called *theine*, which in 1838 was proved by Mulder and C. Jobst to be identical with caffeine. Caffeine is somewhat widely disseminated through the vegetable kingdom, but is commercially chiefly obtained from damaged, or originally very inferior, tea.

#### Official Preparations:

Fluidextractum Guaranæ.....	1 to 2 fluidrachms (4-8 C.c.).
Caffeina.....	1 to 3 grains (0.06-0.2 Gm.).
Caffeina Citrata (a mixture of equal parts of Caffeine and Citric Acid).....	2 to 5 grains (0.12-0.3 Gm.).
Caffeina Citrata Effervesces (2 per cent.)...	1 drachm (4 Gm.).
Pulvis Acetanilidi Compositus (10 per cent.)	.5 grains (0.3 Gm.).

*Local Action.*—*Absorption and Elimination.*—Caffeine is not irritant, and for practical purposes may be considered to have no local action, except it be upon the sensory nerves. It is absorbed rapidly; eliminated chiefly through the kidneys, when in large amount in part unchanged, when in small quantity entirely altered (Richard Schnei-

\* See Moulton (*J. A. M. A.*, Nov. 1901); Swan M. Burnett (*T. G.*, Dec. 1901); F. Buller and Casey A. Wood (*J. A. M. A.*, Oct. 1904); also Von Graefe (*Arch. f. Ophth.*, Bd. lii.; Bd. liv.).

der, also E. Rost). According to M. Albanese, at least a part of the caffeine (trimethylxanthine) appears in the urine as dimethylxanthine, monomethylxanthine, or even xanthine.

*General Action.*—The peculiar wakefulness, the increased mental activity, and the nervous restlessness which are induced by strong coffee are familiar phenomena to almost every one. They are without doubt largely, if not altogether, due to the caffeine contained in the beverage.\* By doses of four or five grains of the alkaloid a somewhat similar state of body and mind may be induced. Lehmann found that eight grains of caffeine produced increased frequency of the pulse, very frequent urination, tremulousness, excited mental action, passing into a form of delirium, with confusion of thought, visions, and finally a deep sleep. About two hours after taking twelve grains, Pratt was seized with intense physical restlessness, conjoined with a very uneasy condition of the mind; very marked general muscular tremulousness soon followed, and the mental anxiety increased. After this state passed off, there was obstinate sleeplessness, with active and persistent thinking, and frequent urination.

According to various observers, the chief symptoms induced by poisonous doses of caffeine in the frog are muscular quietness and weakness, with disturbance of respiration, succeeded by a stage of violent tetanic convulsions, ending in general paralysis and asphyxia, the heart beating after the cessation of respiration, although evidently much affected.†

In birds poisoned with caffeine the symptoms (Brill) are irregular movements, apparently to some extent due to cerebral disturbance, increased rapidity and irregularity of respiration, spasmodic tremblings, and tetanic and clonic convulsions, with paralytic phenomena. In mammals the results of the toxemia, as noted by various observers, are restlessness, hurried respiration, at first a slight lowering and afterwards a decided elevation of temperature, muscular weakness, tetanic and clonic convulsions, increasing general paresis, and finally death, apparently from paralytic arrest of respiration.‡

\* The belief that caffeine and theine act dissimilarly upon the normal organization is no longer open to difference of opinion. For discussion and literature see p. 317, Eleventh Edition of this work.

Whether the other substances found in the coffee bean play any part in its physiological effects is not yet certain. The investigations which have so far been made have been so inharmonious as to forbid satisfactory summary, so we dismiss the subject with the following key to the literature: Erdmann, (*A. E. P. P.*, 1902, vol. 48); E. T. Reichert (*Med. News*, 1890, vol. 56); Binz (*C. I. M.*, 1900, vol. 21); Archangeleski (*A. I. P. T.*, 1900, vol. 7).

† See Albers (*Deutsche Klinik*, 1853, 370), Falck and Stuhlmann (*Virchow's Archiv*, xi. 334), Mitscherlich (*Der Cacao und die Chocolate*, Berlin, 1859), I. Hoppe (*L'Echo Méd.*, 1858), Brill (*Inaug. Diss.*, Marburg, 1861), Oscar Johannsen (*Inaug. Diss.*, Dorpat, 1869), and others. The minimum fatal dose is stated by Leven (*Arch. de Physiol.*, 1858) to be .015 grain in a frog of moderate size.

Johannsen denies the existence of true convulsions in the frog, asserting that there is only a rigidity due to an effect upon the muscles.

Buchheim and Eisenmenger (quoted by Schmiedeberg) corroborate the muscular changes noted by Johannsen, but insist that there are also true nervous convulsions. O. Schmiedeberg (*Archiv für Exper. Pathol. und Pharm.*, ii.) believes that he has reconciled these differences of observation by finding that the alkaloid acts much more powerfully upon the muscles of *Rana temporaria* than upon those of *Rana esculenta*; so that a dose of caffeine which causes intense general muscular stiffness in the former produces in the latter only true convulsions, the convulsions in *R. temporaria* being prevented or masked by the disorder of the muscles. More recent researches (E. Leblond, *La Caffeine*, Paris, 1883; W. Filehne, *Arch. f. Anat. und Physiol.*, 1886) indicate, however, that the differences depend to some extent upon the size of the dose, but in still greater degree upon variations in the sensitiveness of individual frogs; thus, Kobert (*Arch. f. Exper. Path. u. Pharm.*, xv.) found that frogs of the same species are very much more susceptible in the spring than in the autumn. The rigidity and paralysis are muscular.

‡ In an elaborate series of experiments, Bennett (*British Medical Journal*, 1874) found that the fatal minimum dose of the poison for the cat and the rabbit was a little over a grain for the pound, five and a half grains being required for a five-pound animal.

*Cerebrum*.—There is no evidence that caffeine exerts a very marked influence upon the cerebrum of the frog, or even of some of the lower mammals, unless the convulsions induced by it are believed to be partly the result of some such action. In certain of the higher animals, such as the cat, it often produces a condition of almost frantic cerebral excitement. In man the increase of brain-power produced by coffee, tea, guarana, and other drugs containing caffeine and the allied alkaloids is undoubtedly real, and we must conclude that caffeine is a powerful *stimulant to the cerebral cortex*. It appears to us to be our most certain and effective stimulant of the nerve-centres connected with the intellectual functions. Those centres whose function is consciousness are greatly stimulated, and wakefulness results; while again, in contrast with opium, caffeine increases the activity and power of the reasoning faculties at least as much as it does that of the imagination. Coffee prepares for the active work, both mental and physical, while opium leads its votaries to the dream-land of poets.

*Spinal Cord*.—There has been much discussion as to the method in which caffeine produces convulsions in the frog, but it seems to be established that they are, at least in part, of spinal origin. They are not prevented by section of the cord high up (Pratt and Leblond), therefore they are not cerebral; they are prevented by destruction of the spinal cord (Leven), and would appear, therefore, to be spinal.

The difficulty of interpretation of the phenomena has arisen from the fact that the muscular action of the alkaloid in a measure masks its influence upon the spinal cord, there being both muscular stiffness of purely muscular origin and convulsions of spinal origin. This was clearly demonstrated by Pratt, who found that though destruction of the lower portion of the spinal cord prevented the convulsions in the hind legs of the frog, it did not interfere with the development of the contractions. Further, Pratt included all the tissues of a frog, except the spine, in a tight ligature just above the bifurcation of the aorta, and administered caffeine, when the anterior legs became very stiff, and had also occasional severe convulsions, in which the hind legs participated, although between the paroxysms they were perfectly relaxed.

The conclusion seems established that in the frog caffeine *acts as a motor spinal stimulant and also as a muscle-poison*.<sup>\*</sup> The physical restlessness and tremulousness produced in man by excessive doses of coffee and tea, and the convulsions of caffeine-poisoning, are probably both spinal and cerebral, though our knowledge of this matter is incomplete.<sup>†</sup>

*Nerves*.—The motor nerves appear not to be affected, but the sensory nerves are apparently slightly affected.

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<sup>\*</sup> Alexander Bennett has brought forward the theory (*loc. cit.* and *British Medical Journal*, 1874) that caffeine paralyzes the posterior columns of the cord without affecting the anterior columns; but his evidence appears to us insufficient to prove his conclusions. He grounds his belief chiefly on finding that in poisoned frogs and rabbits galvanization of the posterior columns of the exposed cord produced either no muscular contractions or only such as were very much more feeble than those provoked by galvanization of the anterior columns.

<sup>†</sup> Uspensky (*Reichert's Archiv*, 1868, 526) has found that forced artificial respiration in great measure suspends the convulsions.



Alexander Bennett has found that after death from theine the motor nerves retain their normal susceptibility, and Pratt surrounded one crural nerve of a frog with a paste "of theine and water," and irritated the spinal cord, when both legs responded with uniform alacrity. Bennett also tied the crural artery of a frog, poisoned it with the alkaloid, and found that irritation of the cord produced equally active contractions in the two legs. The chief evidence as to the sensory nerves is furnished by Pratt, who found that when the left sciatic nerve of a frog was surrounded by a paste of theine and water, after ten minutes irritation of the right foot produced reflex movements, while irritation of the left foot failed to elicit any response. Leblond has noted marked hyperesthesia in the frog, and Rumpf affirms that increased sensibility of the skin can be demonstrated in man.

*Muscle.*—The action of caffeine upon the muscle is readily demonstrated by throwing the isolated gastrocnemius of the frog into a one-per-cent. or even weaker solution; in from two to three minutes the muscle becomes markedly contracted, swollen, round, stiff, and unable to respond to the galvanic current. That it is the muscle-fibre which is affected is shown by the experiments of Pratt, who found that when an isolated muscle was soaked in a solution of curare until the nerves were killed, and then thrown into a solution of caffeine, the usual rigidity was developed. The elaborate studies of Leblond appear to prove that there are two stages (as in veratrine-poisoning) in the action of caffeine upon the frog muscle,—a primary stage, with exaggerated muscular excitability and a tendency to prolonged tetanic contractions after momentary stimulation, and a final stage of rigidity and lost excitability.\* W. Sobieranski believes that his ergographic experiments prove that in fatigue caffeine not only stimulates the nervous system and thereby increases working power, but also acts directly upon the muscle.

According to the researches of Paschkis and Pal, it would appear to be the xanthine which influences the muscle-fibre, since these investigators found that caffeine (trimethylxanthine), theobromine (dimethylxanthine), and xanthine shared the activity; caffeine being the strongest, xanthine the weakest.

*Circulation.*—When given in a moderately large dose caffeine produces a marked increase in the rate of the pulse with an elevation of the blood-pressure. The increase in the pulse-rate is probably due to the stimulation of the cardio-accelerator mechanism, while the rise of pressure seems to be attributable to a stimulation of both the cardiac and arterial muscles.

According to Voit (quoted by Brill), in the frog the rapidity of the cardiac pulsation is at first increased, but the pulsations become slower and slower, and are accompanied by irregularity of rhythm, the heart finally ceasing to act, but still responding to stimuli at a time when the voluntary muscles are absolutely dead. Falk and Stuhlmann, and Johannsen observed that caffeine first increases and then lessens the frequency of the cardiac pulsations in the frog. According to Johannsen, the lessening of the frequency comes on the more quickly and the more powerfully as the size of the dose is increased. After a time the heart begins to beat irregularly, with short intermissions, which, as time goes on, grow longer and

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\* Johannsen states that when a muscle under the microscope is touched with caffeine its fibres can be seen to contract half their length.

longer, till at last movement ceases. Johannsen found that the action upon the cut-out frog's heart was the same upon the viscus *in situ*; Leblond confirms this, and states that the heart is finally arrested in systole; so also does Thomas J. Mays. Aubert and Haase find that the action of the alkaloid upon the pulsations of the frog's heart varies greatly; and indeed the individual experiments of the authors previously quoted show such variation. This is confirmed by the research of Rioschiro Maki. This investigator experimented upon the cut-out frog's heart with the Williams apparatus, and found that the pulse was variously affected. In most of his experiments the arterial pressure—*i.e.*, the heart's work—was markedly lessened, but in a few cases it was distinctly increased.

Paul Faval finds that in a proportion of ten centigrammes to one hundred and fifty grammes of artificial blood the alkaloid reinforces the isolated frog's heart, giving its contractions more amplitude and more energy, but that stronger doses depress the heart, and finally arrest it in diastole; and H. C. Beyer has reached similar conclusions with the terrapin's heart.

*Mammal.*—The results obtained by various experimenters as to the influence of caffeine on the circulation in mammals are in their general appearance contradictory, but are, however, we believe, reconcilable.

In attempting such reconciliation it seems better to discuss separately the effects of the drug upon arterial pressure and pulse-rate. In the Aubert and Haase experiments, caffeine usually produced pronounced fall of the arterial pressure, although in one experiment there was a distinct rise. It is to be noted that the research was made with enormous doses of caffeine, and usually upon dogs under the influence of narcotics. In two experiments upon alcoholized dogs, Binz obtained a pronounced rise of the arterial pressure; while Maki, experimenting upon animals under the influence of atropine or chloral, obtained after large doses a distinct fall of the arterial pressure, which in a few cases was preceded by a rise. It is evident that the method of research employed in these experiments makes it impossible to draw any very positive conclusions. In normal animals, Leven found in the first stages of caffeine-poisoning a distinct increase of the arterial pressure, and in the elaborate experiments of Reichert it was noted that in the normal dog caffeine injected into the jugular vein, in moderate amount, caused a primary fall of pressure (evidently due to an overwhelming effect of the concentrated alkaloid upon the heart), followed by a rise above the norm, followed in turn, if the dose had been large enough, by a marked fall of pressure. Very large doses of caffeine produced a persistent fall of pressure, ending in final diastolic arrest of the heart. In none of Reichert's experiments was the rise of arterial pressure very great, but, except after heavily toxic doses, it occurred almost invariably. Leven asserts that after he had divided the pneumogastrics and sympathetics and isolated the heart from all the nerve-centres, caffeine still increased the arterial pressure; while Reichert states that not only is the increase of the pressure seen when the animal is motionless with curare, but also after destruction of the vaso-motor centres in the medulla oblongata. Loewi in oncometrical experiments on the intestines failed to obtain any evidences of the contraction of these vessels with caffeine and believes that the rise of blood-pressure is purely cardiac. Experimenting on the isolated mammal heart, Bock found that though there was a continual increase in the rate of the pulse in the majority of the experiments the pressure exerted by the left heart was lowered, although in a considerable minority it was first elevated, especially when a small dose of the caffeine had been given. Bock concludes from these experiments that the elasticity of the heart-muscle is diminished by caffeine, and that the elevation of the arterial pressure naturally produced by caffeine in the normal animal is due to contraction of the blood-vessels. The method of experimentation seems to us very uncertain, and the result is in direct discord with other experiments already cited.

The total evidence seems to us conclusively to show that caffeine increases the arterial pressure independently of the vaso-motor centres.

In the advanced stages of caffeine-poisoning both the heart and the vaso-motor system are without doubt depressed, so that the cause of the fall of pressure is duplex.

In regard to the *pulse*, Aubert notes as a constant effect an increase of the pulse-rate, and this appears to be the most frequent result produced by caffeine; but it has been shown by Reichert that under certain circumstances there is a slowing of the pulse.

Leven asserts that the increase of the pulse-rate is to be seen after isolation of the heart from the nervous centres, and is, therefore, due to an action upon the heart itself, a conclusion which is in accord with the general results of observations upon the isolated frog's heart, and is confirmed by Reichert, who believes that there are paralyses of the cardio-inhibitory centres, both in the medulla oblongata and the heart. The slowing of the pulse occasionally seen in the first stages of the poison Reichert attributes, with probable correctness, to a primary stimulation of these cardio-inhibitory centres; the alteration of the pulse, which sometimes occurs in advanced poisoning he believes to be due to a direct action of the drug upon the heart. Bock believes that the frequency of the pulse usually produced by caffeine is the outcome of powerful stimulation of the cardiac accelerator apparatus, and that the inhibitory apparatus is not depressed, basing the latter belief on the fact that he has observed that section of the vagi in the poisoned animal still further increases the rapidity of the pulse whose rate is already much above the normal.

*Diuretic Action.*—In poisoning by caffeine great increase in the secretion of urine is a common symptom, and the statement of Gubler that the alkaloid is one of our most powerful and certain diuretics, has received abundant confirmation. The effect of the drug upon healthy men would indicate that it does not act simply by regulating the circulation of the kidney, but has also a distinct effect upon the renal organ itself.

That caffeine acts directly upon the kidneys was proved by W. von Schröder and by A. Langgaard, who separately found that when a cannula was inserted into the ureters in an animal whose vaso-motor system was completely paralyzed by chloral, injections of caffeine into the circulation caused a very great increase in the urinary secretion. Langgaard found that usually before the great increase of diuresis the urinary secretion was arrested for several minutes. This is in exact accord with the experiments of C. D. T. Phillips made with Roy's oncometer. It was found that immediately after the injection of a small dose of caffeine, when the blood-pressure was either slightly depressed, elevated, or unaffected, the kidney underwent a very distinct contraction of its volume, which lasted for two or even three minutes and was accompanied by great lessening or arrest of the urinary secretion. After the contraction, the kidney rapidly expanded beyond its original bulk, and at the same time the urinary secretion became excessive. Loewi found that caffeine is capable of dilating the blood-vessels after division of the renal nerves and believes that the increased activity of the kidneys depends upon vascular dilatation. These facts do not prove, however, that the diuresis is caused by the increased flow of blood to the kidneys. It is more probable that the dilatation of the vessels is the result, rather than the cause, of the increased secretion. Because the secretion from the uninjured kidney was increased much more than from the kidney whose nerves were destroyed, Schröder believes that the drug increases diuresis by acting both upon the nerve-centres and upon the secreting structure of the kidney. To our thinking, however, the direct injury to the secreting apparatus of the kidney by division of the renal nerves is sufficient to account for the difference between the influence of the alkaloid upon the normal and the operated-upon kidney, without necessitating the theory of a twofold action. Schröder found that



there was an increase not only of the liquid, but also of the solids of the urine. Anten believes that caffeine increases an inhibitory influence of the pneumogastric nerve on the kidney, thereby interfering with its non-excretive influence, a theory which seems to us extremely doubtful.

*Temperature.*—We know of no recorded temperature-curves of caffeine-poisoning in man. It is probable, however, that the effect of the alkaloid is precisely what it is in other mammals. Binz states that in animals minute doses have no effect upon the bodily temperature; doses just enough to produce slight toxic symptoms cause a rise of  $0.6^{\circ}\text{C.}$ ; excessive doses cause an elevation of  $1^{\circ}$  to  $1.5^{\circ}\text{C.}$ , the maximum being reached in one to two hours; doses which rapidly kill have very little effect upon the temperature.

*General Nutrition.*—The enormous use made by mankind of substances containing caffeine indicates that in some way it is directly of service in the wear and tear of daily life. The experimental evidence, however, although not conclusive, does not point towards any marked effect of the drug on metabolism.

This subject was laboriously investigated by Julius Lehmann in 1853, and by F. W. Böcker in 1854, and earlier. Lehmann found that the exhibition of six grains of caffeine daily, the regulated diet being uniform, diminished the elimination of urea from twelve to twenty per cent. Upon experimenting with the empyreumatic oil of coffee he found that it lessened even to a proportionately greater extent the elimination of urea, and also acted very powerfully in producing sleeplessness, so that the favorite beverage is by no means dependent upon its contained caffeine for all of its activity. Böcker published his first researches on coffee in 1849, but we have never seen any abstract of the article, other than the statement that he found that the drug causes diminished elimination of urea. His investigation of the effect of tea was most elaborate and laborious. He analyzed the feces, the urine, and the products of respiration, and found, a similar diet being maintained, that tea did not affect sensibly the elimination of carbonic acid from the lungs, but did very decidedly diminish the excretion of urea, and also of nitrogenous matters in the feces. He then tried abstaining from food for periods of thirty-six hours, with and without the use of tea, with results perfectly in accord with those just stated. The results obtained by other experimenters are, however, singularly discordant. Henri Hoppe found that, in the dog, coffee diminishes very slightly the urea-elimination, but greatly increases the output of carbonic acid. In regard to urea, Rabuteau and his pupil Eurastriade, working with coffee upon men and dogs, obtained results similar to those of Böcker, as did also Hammond in this country. On the other hand, C. G. Lehmann, Voit, and Roux found that caffeine or coffee sensibly increases the elimination of urea, or, in those accustomed to the daily use of coffee, has no influence. In a long series of experiments upon dogs by Couty, Guimaraes, and Niobey, it is affirmed as a uniform result that the use and assimilation of nitrogenous food were greatly increased, that the carbonic acid and oxygen in the blood were markedly decreased, and that the proportion of sugar and of urea in the blood was notably increased.

In the face of so much contradiction it is perhaps wisest to reserve opinion, but it does seem as though the present evidences warranted the conclusion reached by E. Periset that the action of caffeine upon urea-elimination and upon protoplasmic change is inconstant, and not direct and pronounced. It is true that in a long series of very elaborate calorimetrical experiments performed by E. T. Reichert it seems to have been proved that caffeine increases the heat-production as well as the heat-dissipation, and that of these phenomena, the increase of the heat-production is probably primary. This result is in accord with that of Wilhelm Heerlein, who found marked increase in the consumption of oxygen and formation

of carbonic acid produced under the influence of caffeine. Nevertheless, these united results, if their accuracy be accepted, do not show that destructive metamorphosis of nitrogenous tissue is increased by caffeine, but only that there is an increased destruction of carbohydrates.

**SUMMARY.**—Caffeine is a powerful stimulant to those cells of the cerebral cortex which are functionally connected with consciousness and intellectual action. It is also mildly stimulating to the respiratory centres and probably to the motor cells of the spinal cord, but seems to be without action upon the nerve-trunks. It is a powerful muscle-poison, at first producing a condition in which there is exaggerated muscular excitability, with a tendency to tetanic contractions upon momentary stimulation, and afterwards a stage of stiffness, weakness, and finally, lost excitability. It is a mild stimulant to the circulation; probably by virtue of its relation to the muscle-fibres it increases the cardiac force and perhaps also directly contracts the arterioles. In overdose it depresses the circulation, probably acting both upon the heart and the blood-vessels. It is absorbed with rapidity, and is to some extent decomposed in the body, and at least in part, eliminated through the kidneys, upon whose secreting structure it exerts a marked stimulating influence. Although the evidence is contradictory, it is not at present writing probable that caffeine has any distinct specific influence upon protoplasmic nutrition, but it does appear to directly increase the production of carbonic acid and of animal heat.

**Therapeutics.**—In accordance with its physiological action, caffeine is employed in practical medicine as a cerebral, renal, respiratory and cardiac stimulant. It is often taken to produce wakefulness and increase the mental power during excessive work. It is a valuable remedy for the relief of *migraine* and other forms of *nervous headaches*, in which its effects are sometimes marvellous, although more often it fails to accomplish good. To predict in any case what its influence will be, in the present state of our clinical knowledge, is impossible; but the remedy may always be tried in safety in the dose of five grains, taken when the paroxysm is coming on, and repeated in half the quantity once in forty minutes if necessary. It is in these cases especially effective in combination with acetphenetidin (proportion five grains to fifteen grains). In *opium-poisoning*, either in the form of unlimited quantities of a strong decoction of coffee or of the alkaloid itself, it is a standard remedy, acting by promoting wakefulness and stimulating the respiration.

J. Hughes Bennett found that the exhibition of from four to four and a half grains of caffeine would save a proportion of cats poisoned with the previously ascertained minimum lethal dose (one and seven-eighths grains) of morphine. Several of the cats which had thus been saved succumbed some days afterwards to one and seven-eighths grains of morphine. The caffeine was powerless to save animals to which larger doses of the narcotic had been given.

We have had no experience with the use of caffeine as a general stimulant in *acute adynamia*, but various French authors recommend

the remedy very highly, and H. Huchard especially commends it in *typhoid fever*, asserting that it relieves not only the adynamia, but also acts as an antipyretic, and through its diuretic influence is especially useful when the urine is scanty and albuminous.

As a circulatory stimulant caffeine is, although a remedy of but slight power, at times a valuable adjunct especially in the acute forms of circulatory failure. In chronic *heart disease* it does not exercise any tonic effect on the heart-muscle, indeed it is probable that its stimulant action is wasteful of the heart power; so that it cannot be compared with digitalis in either degree or kind of action.

On account of its diuretic action it may frequently be employed, with much benefit, in cases of circulatory weakness accompanied by *dropsy*. In chronic *Bright's disease* it is often of service, especially in the latter stages, when there is marked cardiac failure. In *acute Bright's disease* it should be employed with caution, if at all. It is superior to digitalis in never disagreeing with the stomach and in having no distinct cumulative tendency. In some cases, however, it produces obstinate wakefulness, and we have occasionally found it necessary to give it solely in the early part of the day. It is usually best to commence with a dose of four grains, given twice daily, increased if necessary to twenty or twenty-five grains a day.

**Administration.**—For internal administration the citrated caffeine is often preferred on account of its solubility. When great promptness of action is required, as in cases of sudden *collapse* or of sudden *cardiac failure*, the hypodermic use of caffeine suggests itself. Unfortunately, the ordinary salts are decomposed in the presence of water, and are, therefore, ineligible for hypodermic use. The *sodium and caffeine benzoate* has been proposed as moderately stable and free from irritating properties. One equivalent of sodium salicylate (160 parts) will also cause the solution of one equivalent of caffeine (244 parts), and the following formula has been commended by Tanret for hypodermic use: sodium salicylate, thirty-one parts; caffeine, forty parts; distilled water, sixty parts.

**Toxicology.**—The only case of poisoning by caffeine that we have met with is reported by C. H. F. Routh. An adult took a drachm of the so-called citrate. The symptoms developed at once; they were burning in the throat, giddiness, faintness, nausea, numbness and tremors of the extremities, pain in the stomach and bowels, profuse diuresis, and finally collapse, with cardiac oppression and icy extremities. Consciousness was not impaired, and there was no headache until the patient began to recover. In a case reported by Curschmann, a woman, in order to produce an abortion, took a decoction made from about eight ounces of freshly roasted coffee. Two hours later she was found in a condition of great anxiety, with a sensation of intense need for air; she was exceedingly restless, and continually attempted to get up from her chair, but was powerless to do so. All the extremities, but especially the hands, were affected with very pronounced choreic tremors. She knew persons and her



surroundings, but her cerebration was very much affected, and the next day she remembered nothing that had happened at this time. The respiration was quick, 24 and 25 per minute, and short; the pulse 112; the heart-beats very strong, even violent. One hour after the ingestion of the dose violent diarrhœa set in, and continued until the next day. The passages were very thin and watery, with but little violent pain, but much tenesmus. There was also marked tenesmus of the bladder. The urine was greatly increased in quantity, with a specific gravity of 1014. P. B. Wing has reported a case of amblyopia produced by the excessive use of coffee.

### DIGITALIS.

Digitalis is the leaves of the *Digitalis purpurea*,\* or foxglove, a European perennial plant, largely cultivated for its beautiful purple, bell-like flowers. The leaves, which should be collected during the second year of the plant's growth at the commencement of flowering, are of a dull pale green with a whitish down underneath, from four to twelve inches in length and have a bitter nauseous taste and faint narcotic odor.

Our chemical knowledge of the active principles of digitalis is far from satisfactory. According to the latest investigations there are at least three active glucosides found in the digitalis leaves. These are *digitalin* (of Kiliani), *digitoxin* and *digitonin*. The substance described by Schmiedeberg under the name *digitalein* has not received general recognition as a pure principle. Digitonin differs markedly in its action from the other principles of digitalis and appears to belong to the saponin group of principles. It exists in such small quantity in the drug as to have very little effect upon the total action of digitalis.

The term *digitalin* has been applied to a number of substances. Digitalin of the French Pharmacopœia is generally considered an impure form of digitoxin. The substance commonly understood in this country by digitalin is the so-called German digitalin (*digitalinum Germanicum*); this is not a pure principle but consists chiefly of digitonin and depends for its activity probably upon true digitalin; it is asserted also to contain some digitoxin.

#### Official Preparations:

Digitalis.....	1 to 3 grains (0.06–0.20 Gm.).
Extractum Digitalis.....	$\frac{1}{2}$ grain (0.016 Gm.).
Fluidextractum Digitalis.....	1 to 3 minims (0.06–0.20 C.c.).
Tinctura Digitalis (10 per cent.).....	5 to 20 minims (0.3–1.3 C.c.).
Infusum Digitalis (1.5 per cent.).....	1 to 4 fluidrachms (4–15 C.c.).

#### Unofficial Preparations:

Digitalinum Germanicum.....	$\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008–0.016 Gm.).
Digitoxin.....	$\frac{1}{200}$ to $\frac{1}{100}$ grain (0.3–0.6 Milligm.).

\* The question whether other species of *Digitalis* have the therapeutic properties of *D. purpurea* is of great interest. H. Goldenberg (*Inaug. Diss.*, Dorpat, 1892) states as the results of his experiments that *D. nervosa*, Stend., *D. gigantea*, Fisch., *D. eriostachys*, Linn., *D. fontanesii*, Stend., and *D. glandulosa* all possess more or less of the physiological properties of the official species, while *D. ferruginea*, Linn., is ten times as powerful as the official drug.

*Local Action.*—Locally, digitalis is probably a feeble irritant, although there is some reason for believing that the gastric disturbance which frequently follows the administration of the drug in full doses, and which sometimes interferes greatly with its usefulness, is at least in part of centric origin.

*Absorption and Elimination.*—Digitalis yields its active principles to absorption in the intestinal tract with the greatest slowness and with some irregularity, hours usually, and sometimes days, elapsing before the full effect of the dose taken by the mouth is produced. Even when the drug is given hypodermically the slowness of its absorption renders it an unreliable remedy in emergencies. Concerning the fate of its active principles in the body we have no positive knowledge. The experiments of G. H. Roger indicate that they are not destroyed in the liver, and they probably escape from the system through the kidneys.

*Physiological Action.*—The first evidences of the effect of moderate doses of digitalis are an increase in the force and a slowness in the rate of the pulse, the pulse-wave becoming extremely large and hard. If the doses be increased, dirotism develops, and increases until the pulse becomes rapid, broken, irregular, and feeble. During all this period no symptoms are ordinarily produced; after toxic doses, however, there are gastric uneasiness or vomiting, lassitude, prostration, muscular tremors, lowered reflex activity, and sometimes convulsions. (See also *Toxicology*.)

*Nervous System.*—Upon the cerebrum digitalis has no influence; indeed, its effects upon the nervous system are everywhere so feeble that they are not apparent except after the very largest toxic dose.

As was first pointed out by A. Weil, digitalis first lessens reflex activity by directly—*i.e.*, independently of its action on the circulation—exciting the inhibitory reflex centres of Setschenow, and after a time by directly paralyzing the spinal cord.

Weil's experiments were in two series. In the first series it was found that after small toxic doses of the poison great diminution in the reflex activity of the frog was apparent in from ten to twenty minutes, and continued until death of the batrachian, but that this diminution for from twenty-five minutes to an hour was immediately suspended by section of the cord high up, the reflex activity returning at once to its normal state; that after large doses the reflex movements were almost abolished in five minutes, and continued so until death, but at any time during the first ten or twenty minutes they could at once be restored by section of the upper cord; and that, both after large and after small toxic doses, a time finally came when division of the cord had no power to restore the lost reflex functions. These experiments have been confirmed by Meihuizen. In Weil's second series of experiments it was proved that the action of digitalis upon the inhibitory reflex centres and the cord is direct. In these experiments the hearts of frogs were cut out, or their motion arrested by the local application of a concentrated solution of potassium nitrate, or rendered slower by a dilute solution of the same salt, and the effects of these various procedures upon the reflex activity were studied. It was found that slowing of the heart's action did excite the Setschenow's centre, but not to nearly so great an extent as did digitalis, and that minute doses of digitalis sometimes stimulated the Setschenow's ganglion and lowered reflex activity before the

heart was sensibly affected. In regard to the spinal cord it was proved that when the heart was killed by the local action of potash the reflex functions of the spinal ganglia remained intact for a much longer period than when digitalis was administered.

*Muscles.*—That digitalis has some influence upon the voluntary muscles has been proved by the researches of Vulpian, of Dybkowsky and Pelikan, and of Gourvat, all of whom have found that the muscles of frogs poisoned with digitalis respond more freely than is normal to galvanic currents. This action upon the voluntary muscles is, however, so feeble that according to Gourvat it is distinctly less than the influence exerted upon the nerves. There is some reason for believing that digitalis affects also the non-striated muscle-fibres throughout the body.

*Circulation.*—When introduced into the blood stream, in moderate doses, digitalis produces a marked slowing of the pulse with a great increase in the size of the pulse-wave and a considerable elevation of the blood-pressure. After toxic doses the pulse later becomes exceedingly rapid and irregular, the blood-pressure rises to an extraordinary height, which it maintains until the sudden cessation of the heart produces an abrupt fall of the pressure. The slowing of the pulse is due chiefly to stimulation of the inhibitory mechanism, both centrally and peripherally. This inhibitory stimulation, in some cases, may be so excessive as to largely counteract the vaso-motor effect of the drug, the blood-pressure being in this case but very slightly elevated. In the majority of cases, however, the rise of the blood-pressure is very marked. This elevation depends in part upon the narrowing of the blood-vessels through stimulation of the vaso-motor centre, but chiefly upon the increase in the force of the heart.

If the heart is directly observed (see Fig. 13, page 239) during the action of digitalis, the first effect noted is usually the prolongation of the period of diastole caused by the stimulation of the inhibitory mechanism, but about the same time it can be observed that the ventricular systole is more vigorous and complete than normal, so that the heart chambers are completely emptied of blood. Following this the ventricular systole becomes not only more forcible, but also more prolonged than normal. Sometimes, at this stage of the action, the systole is interrupted by an abortive attempt at diastole, producing the characteristic dicrotic pulse. In the frog, from this stage onwards, the changes in the heart are usually gradually progressive. In the mammal, on the other hand, there usually occurs an abrupt alteration in the cardiac action; diastole suddenly disappearing and the pulse becoming extremely rapid. From this time onwards till the end of the heart movements, the impulse to contract constantly encroaches upon the relaxing impulse so that the diastole becomes more and more imperfect and the ventricle approaches more and more closely to a position of complete permanent systole. In the frog's heart this actually occurs; but according to our observations the heart of the warm-blooded animals always



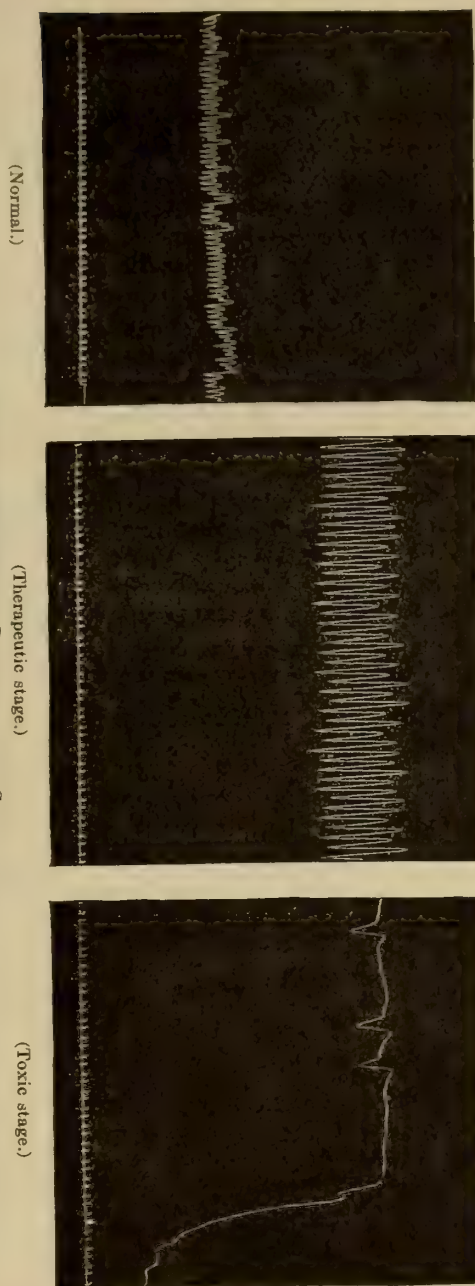


FIG. 12.—THE ACTION OF DIGITALIS ON THE CIRCULATION.  
 Note the slow full pulse with rise of pressure in the therapeutic stage, and the extremely rapid small pulse, due to incomplete diastole with sudden cessation of the heart, in the toxic stage. Time marker indicates 1 second.

relaxes immediately before complete cessation of movement and passes into a stage of fibrillation. Frequently, both in the cold-blooded and in the warm-blooded animals, toxic doses of digitalis produce a condition sometimes spoken of as delirium cordis, in which there is a complete loss of relation between the rhythm of the auricle and ventricle. Although Kaufmann brings forward evidence to show that the auricles as well as the ventricles are stimulated, yet the effect upon the auricles is generally much less than upon the ventricles, and frequently, in the frog, the ventricle may be seen in complete spasm and the auricle engorged with blood and vainly endeavoring to force the fluid into the firmly contracted ventricle.

The effect of digitalis upon the right heart and upon the pulmonary circulation is not definitely determined. The experiments, however, of Bradford and Deane, of Popper, and of H. C. Wood, Jr., indicate that although the drug has some stimulant action upon the lesser circulation it is much less marked than its effect upon the left side of the heart.

The slowing of the pulse produced by digitalis is due to the simultaneous stimulation of the central and peripheral ends of the cardio-inhibitory mechanism. In the advanced stage of digitalis-poisoning, with the extremely rapid pulse, it has been found that electrical irritation of the pneumogastric nerve fails to slow the pulse, showing either a paralysis of the peripheral vagi or such a condition of irritability of the muscle-fibres that they are unable to respond to inhibitory impulses.

*Heart.*—It would appear definitely settled that the cardiac phenomena produced by digitalis are due, in part, to a direct action upon the heart itself.

Boehm and Dybkowsky and Pelikan have found that the slowing of the heart's beat, the increased energy of contraction, and the irregularity and final systolic arrest are produced by digitalis after division of the vagi and destruction of the spinal cord. Again, the local application of digitalis at once influences the heart (T. Lauder Brunton). Moreover, R. Boehm, using the method of Ludwig and Coats, has determined that in the isolated frog's heart digitalis slows the rate of the beat but increases the expenditure of power by the heart.

After a large dose the condition of cardiac stimulation is followed by a great lessening in the output of power, which is apparently due to imperfect diastole and consequent non-admission of fluid into the ventricles. The heart is still actually putting forth more force, but this energy is wasted in ineffectual spasm, and does not accomplish work. The experiments of Williams agree with those of Boehm in showing that the cut-out frog's heart actually exerts more than its normal force under the influence of digitalis.

It seems to be clearly established that in poisoning of the mammal by digitalis the heart is arrested not in systole but in diastole, since the fact has been confirmed by Donaldson and Stevens, by Cushny, and by John P. Arnold and Horatio C. Wood, Jr., the latter investigators being well informed of, and meeting Franck's denial of the diastolic arrest. The belief of Cushny, that the differences in the final result in the digitalized batrachian and mammalian hearts are because the mammalian heart is not capable of continuous systole is confirmed by the experiments of Masi, who found that when the frog's heart is warmed to 32° C., digitalis arrests it in diastole, and when the heart of the mouse is cooled, digitalis stops it in systole instead of diastole; while Donaldson and Stevens have shown that the condition of the venous circulation very materially affects the heart-action of frogs.

It does not seem to us, however, that the whole matter has as yet been worked out. Neither the theories advanced by Cushny, that the arrhythmia and peculiar ventricular movements of the third stage of digitalis-poisoning are the results of excessive irritability of the cardiac muscle, and that these and other cardiac phenomena in the last stage of digitalis action are produced by poisons formed in the heart itself by its own action, nor the theory that the advanced phenomena of digitalis cardiac action are largely due to excessive stimulation of the accelerators, appears to us to be established. In our experiments upon the exposed mammalian heart we have seen in the final acts of the digitalis drama happenings so curious and unexpected that at present no proposed theory as to the action of the drug is sufficient.

*Inhibition.*—The cause of the slowing of the heart has been a matter of some dispute. Traube stated that, after section of the vagi, digitalis is in warm-blooded animals, with rare exceptions, incapable of reducing the pulse-rate, and, contrariwise, that when the pulse-frequency has been reduced by the drug, section of the nerves causes an immediate and very marked rise in the rate of pulsation. Klug also affirms that section of the vagi completely does away with the slowing action of digitalis, and concludes that the lessened pulse-rate is entirely due to stimulation of the pneumogastric centres. The bulk of investigators, however, "such as Marme, Ackermann, Bulgari, Schnabl, Popper, and Kaufmann" (quoted from Cushny), have found that section of the pneumogastric does not completely prevent the slowing of the cardiac rate. This would seem to indicate that, in the mammal, digitalis stimulates centrally the inhibitory nerve of the heart, while at the same time also in some other way it decreases the rate of the cardiac pulsations. When to this conclusion is added the fact seemingly established by the separate researches of Ackermann, of Arthur R. Cushny, and of Arnold and Wood, Jr., that the administration of atropine entirely does away with the slowing of the pulse in the mammal, it would appear that this slowing of the pulse is due to a simultaneous stimulation of the pneumogastric centres and of the peripheral inhibitory apparatus in the heart.

It is probable that the comparative effects of digitalis upon the pneumogastric centre and periphery differ in different individuals, the centric influence usually being the most powerful, but in some cases the nerve-ending being even more susceptible to the action of the drug than is the centre; in this way the very pronounced reduction in the pulse-rate occasionally produced by digitalis in the mammal after section of the pneumogastric may be explained as due to an exceptional sensitiveness of the peripheral ganglia of the individual animals under experimentation.

In the advanced stages of digitalis-poisoning in the mammal there appears to be paralysis of the pneumogastric peripheral ending, or else such exceptional irritability of the muscle-fibres that the pneumogastric nerve has lost its control, since at this period galvanization of the pneumogastric does not perceptibly affect the cardiac action (Cushny, Arnold and Wood, Jr., and others).

The action on the inhibitory apparatus in the frog seems to be slightly different from the effect on the mammal.

There is no stage in which stimulation of the vagi does not cause diastolic arrest. Indeed, Dybkowsky and Pelikan have seen galvanization of nerves produce such relaxation in the auricles after the ventricles had already become permanently contracted. Further, Boehm has found that a stimulation of the pneumogastrics which is insufficient to make itself felt before poisoning will, after the exhibition of digitalis, cause diastolic arrest lasting for many minutes.

The peripheral cardiac inhibitory apparatus shares in the stimulant action of digitalis; and as Boehm has found that after section of the vagi diastolic arrest never takes place in frogs poisoned with the drug, it is probable that this rare mode of death is really due to superexcitation of the cardiac inhibitory nerves.

On the other hand, however, it does not appear that the condition of inhibitory excitement is the sole cause of the slowing of the pulse, since Boehm affirms that not only are the partial contractures and the systolic arrest of the heart produced in the atropinized frog by digitalis, but also a slowing of the heart-beat.



The question as to the comparative action of digitalis upon the ventricles and the auricles is one of distinct practical bearing, but cannot at this time be fully answered, although it is probable that the drug affects the ventricles more than it does the auricles. Kaufmann states that he has experimentally proved that the diastolic as well as the systolic intra-ventricular pressure is increased by digitalis, but that the diastolic intra-auricular pressure is slightly diminished. This would indicate stimulation of the auricles as well as of the ventricles. The pressure within the auricles would naturally not be increased, because digitalis does not increase the flow of blood from the lungs into the auricle; on the other hand, the intra-ventricular pressure during diastole would naturally be increased by any increase in the power of the auricle.

Although digitalis does increase the muscular energy of the heart, it seems scarcely possible that the enormous rise of pressure produced by it can be owing to this alone. This *a priori* reasoning has received experimental confirmation from Malan (quoted by Fothergill), Fothergill, Gourvat, and Ackermann, who have found by microscopic studies that the arterioles of the frog's web, or of the mesentery of the rabbit, undergo very marked contraction, even to the partial obliteration of their lumen, after the exhibition of digitalis. Without attaching too much importance to this evidence, the finding of Traube, of Boehm, and of others, that after section of the cord high up the arterial pressure is either elevated not at all or not nearly so much by digitalis as in the normal animal,\* is a strong indication that the drug increases the arterial pressure largely by increasing the peripheral resistance without centric vaso-motor stimulation. There is, moreover, much still weightier evidence of the truth of this conclusion.

It has been demonstrated by Brunton and Tunnicliffe, that during an inhibitory cardiac arrest the blood-pressure sinks much less when digitalis is given than without it. Decisive are the independent, though contemporaneous researches of Ringer and Sainsbury and of Donaldson and Stevens, who, using the method of Gaskell more or less modified, have apparently proved that digitalis acts upon the walls of the arterioles. They destroyed the nerve-centres of a terrapin, excised the heart, and connected bottles in such a way with the blood-vessels that liquids would run through the arteries and come out through the veins. Under such circumstances they noted a marked reduction of the rate of flow when soluble digitalin was placed in the artificial serum. That in the normal mammal, under the influence of digitalis, there is pronounced contraction of the blood-vessels seems also to be proven by the experiments of John C. Hemmeter, made with Ludwig's *stromuhr*, in which it was found that the velocity of the blood-current was markedly decreased by digitalis, though the pressure was increased. R. A. Kobert† in a series of experiments similar in principle to those of Ringer and Sainsbury, but made upon the excised kidney, found that digitalis retards greatly the flow of liquid through the organ, and therefore acts directly upon the coats of the smaller vessels; also that digitalis and the nitrites are mutually antagonistic.

It may be considered as definitely proven that digitalis *has a direct action upon the walls of the arterioles*, but it is highly probable that it *also acts upon the vaso-motor centre in the medulla*. In a series of plethysmographic experiments in which digitalin and digitoxin were employed, Gottlieb and Magnus found that the local action of digitalis upon the blood-vessels is especially manifested in the region of the splanchnic distribution, although contraction even of the volume of the brain of the dog was demonstrated as produced by digitoxin. As it is probable that the splanchnic nerve almost always dominates the general blood-pressure, a special susceptibility to the action of digitalis is not surprising.

\* These experiments have been contradicted by Ackermann, who states that he has many times cut the spinal cord and without exception found a very marked rise of arterial pressure follow the injection of digitalis. Unfortunately, none of these experiments have, that we are aware of, been published in detail, and it is therefore impossible to analyze or to reconcile them; but Görz (*Schmidt's Jahrbücher*, clviii.) expresses the opinion that Ackermann did not fully divide the cord in his experiments. Görz himself found that a rise is produced by digitalin after division of the cord, but of so small an amount as readily to be accounted for by the increased power of the heart.

† Kobert tested two specimens of *digitoxin* and *digitalin* which had been supplied by Schmiedeberg, their discoverer, and found that instead of contracting the vessels of the kidney they actively dilated them and increased the flow of liquid.

*Man.*—According to our experience, decided therapeutic doses of digitalis, in man, produce great reduction of the pulse-rate and sometimes dirotism of the pulse, and increase the size and force of the wave, at the same time augmenting the arterial tension. Poisonous doses induce, after a time, increase of the pulse-rate, with smallness of the wave.

Sphygmographic studies of the effect of digitalis upon persons suffering from various acute and chronic diseases have been made by Legroux, Bordier, Constantine Paul, and Paul Lorrain. The problems offered by these gentlemen are so complex as to render a detailed study almost impossible; but, as a whole, their tracings seem to confirm our personal experience. Paul Lorrain calls attention to the fact that when the drug has reduced the pulse-rate very greatly a second abortive systole can, on auscultation, sometimes be heard occurring during the long diastole, and some of his sphygmographic tracings are markedly dirotic. It is evident that in man the second systolic movement occurs precisely as in animals; and it seems very certain that the proposition framed for the lower mammals applies also to man.

When the pulse has been reduced by digitalis to 40 or 50 a minute, the change from the recumbent to the erect position will not infrequently suffice to alter at once its character, so that it will become small and rapid, even 150 per minute. The explanation of this seems to be that the heart of such a patient is just in the position in which the diastolic impulse is being overcome by the excessive systolic stimulation of the drug. While the patient is recumbent, the line is not passed over, but the additional stimulation of the erect position carries the heart beyond the limit of regular diastole, and the over-effects of the drug are at once manifested.

*Urinary Secretion.*—The influence of digitalis upon urinary secretion in health has been studied by numerous observers, with such diverse results as to prove that the action of the drug on the kidneys is so inconsistent and varying as to render it probable that it is in great measure indirect rather than direct. Thus Jörg, Hammond, and Brunton have found the secretion more or less decidedly increased, and Homolle, Winogradoff, Stadion and, according to Brunton, also Krahmer, Kluyskens, Vassal, and Shohl, have found it either uninfluenced or diminished. Kaufmann has found it uniformly diminished in the dog.

Investigations made upon the action of digitalis upon the elimination of organic matters through the kidneys have yielded such contradictory results that at present the conclusion seems justified that the drug has no consistent dominant influence upon the output either of nitrogenous or inorganic solids through the urine.

The urea in the apparently very careful experiments of Winogradoff, of Stadion, and of Hammond was diminished, while in the almost equally elaborate experiments of Brunton it was increased. All four observers noted lessening of the chlorides. Mégerand, using the crystallized digitalin of Nativelle, found his urine increased twenty-five per cent. but his urea diminished twenty per cent. Auguste Meusnier has sought without success for sugar in the urine both of patients taking large doses of digitalis and of rabbits poisoned with the drug. Kaufmann states that digitalis leaves, or preparations which produce local irritation, cause in the dog an increase in the elimination of urea, but that when digitalin was given in solution the excretion of urea was diminished. G. P. Sereschnikow, as the result of experiments upon man, finds that digitalis has no pronounced constant effect upon nitrogenous elimination. He is confirmed by Alexëvsky, while I. Beljikow asserts that the drug increases the elimination of the chlorides, sulphates, and phosphates.

*Temperature.*—Toxic doses of digitalis lower the temperature a number of degrees in healthy men and animals. It would seem, however, that the fall of temperature is generally, if not always, preceded by a rise, as has been noted by Bouley and Reynal, by Duméril, Demarquay, and Lecointe (quoted by Brunton), by Hirtz, by Legros, and by Gourvat. Kaufmann believes that such rise is due to the local irritation caused by the drug, and asserts that if no irritation be produced there is always in the animal a fall of rectal temperature ( $0.4^{\circ}$ – $0.5^{\circ}$  C.) after even a feeble dose of digitalin.

The effect of *therapeutic* doses in the normal condition has not been closely studied, that we are aware of. But in a number of cases, chiefly of pneumonia, Z. E. Coblentz found that about twelve hours after the fall of the pulse there was also a fall of temperature. The tendency of our present knowledge is to connect the changes in temperature induced by digitalis with the changes of the circulation; and it seems very possible that therapeutic doses in health may be found to increase bodily heat, although in fever they may diminish it.

**SUMMARY.**—It would appear to follow, from experiments upon frogs, that the toxic dose of digitalis primarily inhibits reflex action by stimulation of Setschenow's centre, and subsequently directly paralyzes the motor tract of the spinal cord. This influence is not, however, very apparent, even in the lower mammals, and in the human individual the symptoms of digitalis-poisoning are chiefly manifested in irritation of the stomach and disturbance of the circulation, death finally occurring in collapse, sometimes preceded by delirium, stupor, or convulsions, though consciousness is long preserved. The therapeutic dose of digitalis acts almost solely upon the circulation, slowing the rate and increasing the force of the heart's beat by a direct stimulating action on the pneumogastric nerves and upon the heart itself. By this cardiac influence, and also by contracting the blood-vessels through a direct action upon their walls, and also probably upon the vaso-motor centres, the therapeutic dose of digitalis enormously increases arterial pressure. Probably by its direct influence upon the heart-muscle, and also by stimulating the pneumogastric or trophic cardiac nerve, and by increasing the blood-supply of the heart, in certain diseased conditions digitalis acts not only as a cardiac stimulant, but also as a cardiac tonic. In the frog the heart stops in systolic spasm; the mammalian heart, after going into a condition of fibrillary contractions, ceases all movement in diastole. The active principles of digitalis are absorbed and probably eliminated through the kidneys, though in health the diuretic action of the drug is extremely uncertain. Upon the alimentary canal digitalis acts as an irritant, affecting the stomach more than the intestines, and often, when in full dose, producing gastric pain and vomiting.

**Therapeutics.**—The chief clinical use of digitalis is in diseases of the heart; and from what has been said of its physiological action it logically follows that it should be useful in loss of cardiac power.



When the muscle of the heart is for any reason unequal to the task set it, the systoles become rapid and imperfect, and by this irregular action, the ventricles neither completely filling nor completely emptying themselves, increase the embarrassment. Under these circumstances, digitalis, by lengthening the diastolic pauses and increasing the force of the systolic contractions, causes the ventricles to fill themselves completely in the one and to empty themselves completely in the other act. By subduing irregular action through the inhibitory nerves, and by energizing the muscular power of the heart-walls, the remedy is of incalculable service, and, increasing arterial tension all over the body, causes the disappearance or lessening of symptoms due to low pressure in the arteries.

It is a logical necessity, if our reasoning as to the physiological action of digitalis has led to a correct result, that the drug should be of the greatest service when the lesion is simply loss of cardiac power; and clinical experience tallies with this *a priori* argument. In *simple dilatation*, or in *simple failure of the cardiac muscle* without degenerative changes or valvular lesion, the results of the use of digitalis are most favorable.

On the other hand, in *simple hypertrophy* digitalis does harm, and should never be used. It must be borne in mind that although this agrees with what the experimentalist has proved to be the action of digitalis, yet it was discovered independently as a clinical fact by practitioners. Thus, Niemeyer,—who ridiculed experimental therapeutics because he would not take the trouble to study it deeply and practically and was therefore incapable of understanding it,—says, “Digitalis in pure uncomplicated hypertrophy is unsuitable.”

Valvular lesion of the heart, as is well known, gives rise under unfavorable circumstances to dilatation, but in favorable cases to hypertrophy, or rather in the great majority of cases to hypertrophy with dilatation. Following out the principles already inculcated, it might seem at first that the use of digitalis in hypertrophied hearts with valvular lesion ought to be reprobated. But it is known clinically that digitalis often does good in valvular lesion with enlargement of the heart. The results of logical deductions from our physiological conclusions as premises are, however, not really at variance with this. It must be borne in mind that structural hypertrophy and functional hypertrophy are different things: by this is meant that although a heart be enlarged and absolutely stronger than normal, yet it may be, relatively to the work required of it, *weak*. Thus, if 1 represents the normal work of the heart and 1 its normal power, if the former be increased to 4 and the latter to 3 the heart is really in the position of a weak organ, although possessed of three times its original strength. Hence it is that digitalis is often useful in valvular disease with hypertrophy. In the vast majority of cases the heart with diseased valves is in the position just spoken of; but sometimes the work advances only to 2 and the strength to 3; then the hypertrophy being excessive, digitalis increases the difficulty.

In *mitral insufficiency* and in *mitral stenosis* digitalis is often of great service. It is evident that in both instances the valvular lesion leads as its first result to pulmonic hyperemia. How does the digitalis lessen this? In the case of *stenosis*, the diastole being lengthened by the remedy, the auricle is afforded more time to empty itself into the ventricle through the narrowed orifice, and at the same time is strengthened in its contracting power; evidently, then, the left ventricle when its systole occurs will have much more to contract on than before the digitalis was administered, and the amount of blood in the systemic circulation will be increased,—*i.e.*, the amount in the pulmonic circulation will be diminished; further, the right ventricle will have greater power afforded it to force the blood through the lungs.

In *mitral insufficiency* the mechanism is different, but the result is the same. The increased power of the systole will throw proportionately more blood through the aortic orifice than through the partially open valve. The opening at the insufficient mitral valve is much smaller and more obstructed than the aortic orifice. As the force or rapidity of the current increases under the action of digitalis, the friction becomes greater at both orifices, but the ratio of increase is evidently far higher in the small choked mitral leak than in the wide aortic opening. Hence the large orifice constantly gains upon the smaller as the cardiac force is increased, and more blood passing into the systemic circulation, the pulmonic vessels are relieved. Again, the right ventricle shares the stimulant action of the drug, and acts more strongly upon the pulmonic circulation, resisting the direct backward flow from the auricle. There are cases of mitral cardiac disease in which digitalis seems to be indicated, but when given acts unhappily. In some of these cases the augmented distress is probably caused by a strain upon the auricles. If the ventricle be already too strong for the auricle, and if by virtue of a very patulous mitral valve the backing of the blood upon the auricle is very easy, it is readily understood how increasing the power of the ventricle may augment the auricular strain. Especially is this consideration important in the light of Kaufmann's researches, which seem to show that the ventricle is more affected by digitalis than is the auricle, and hence that a stimulated ventricle may have to be met by a non-stimulated auricle.

In *aortic constriction* digitalis is useful when the heart-power begins to fail. In these cases compensatory hypertrophy, with slowness of action, is very apt to occur, or even to become excessive; much more frequently does this happen than in mitral disease. Again, in *aortic insufficiency* the prolonged diastole of digitalis action favors the return of blood to the heart, and is not advantageous. It is evident that digitalis is not so generally useful in aortic as in mitral disease: nevertheless, when the heart-muscle fails, and the hypertrophy is not compensatory, the drug is useful in both aortic stenosis and insufficiency.

From the considerations which have been brought forward, it is very evident that a knowledge of the relation of the heart-muscle to the work required of it in any individual case is much more necessary to the therapist than to know what valve is diseased.

In "*irritable heart*" of soldiers—a disease or condition of cardiac irritability evidently connected with muscular weakness, and very probably dependent upon exhaustion of the inhibitory nerves—Da Costa found that in the early stages of the affection digitalis not only acted better than any other remedy, but even, when administered continuously for some time, often effected a permanent cure. When hypertrophy had taken place, the drug was of little use.

The relief afforded by digitalis in not too inveterate cardiac disease is often in a measure permanent, because the drug may aid very materially in the production of compensatory hypertrophy. Dilatation is certainly more likely to occur when the muscular fibre is lax and acting feebly than when it is toned up and in vigorous play; secondly, the stimulus to action in a muscle is almost of necessity directly or indirectly a stimulus to its nutrition; thirdly, it appears probable from the researches of Gaskell that the period of inhibition is one of structural upbuilding, and that therefore the pneumogastric nerve is trophic in its nature, so that it is probable that digitalis, by stimulating the trophic cardiac nerve, benefits the cardiac nutrition. Lastly, improved systemic circulation means in a far more intense degree improved blood-supply to the cardiac muscle, because the coronary arteries being comparatively small vessels springing almost at right angles from the aorta, the tendency of the blood is to flow onwards; consequently a considerable degree of pressure in the aorta as well as resistance in the peripheral vessels is necessary for the proper filling of the coronary circulation and nutrition of the heart. These conditions are peculiarly favored by the big slow pulse of digitalis and by the vascular constriction.

That digitalis exerts the nutrient and trophic influence here set forth has been strongly confirmed by the research of Hare and Coplin, in which it was found that the continuous giving of digitalis to young pigs produced a distinct increase in the size and weight of the heart as contrasted with control animals of the same litter.

If in *aneurism*, or in general *capillary atheroma*, there be increased resistance to the circulation, and the heart have not sufficient power to meet this, digitalis may be useful, but must be employed with caution. It not only increases arterial pressure, but also causes the pulse-wave to be of enormous size as well as power, so that there is great danger of distending and tearing open the thinned wall of an aortic aneurism. The use of digitalis for the purpose of "quieting the circulation" in aneurism is very dangerous. We have seen immediately fatal hemorrhage produced thereby.

In *cardiac dropsy* digitalis is of service probably not only by regulating through the heart the circulation, and by evacuating the surplus fluid through the kidneys, but also by an action upon the



vessels, vaso-motor weakness being evidently a strong factor in the production of dropsy.

In *endocarditis* and in *myocarditis* with marked irregularity of the cardiac action and failing power there is naturally a strong impulse to the administration of digitalis. It should be remembered, however, that in an acute inflammation of the lining membrane of the heart the action of the heart is often really of the nature of an excitement, and that therefore, it would *a priori* be expected that digitalis would do harm rather than good. Restrained by this belief, we have never used digitalis boldly in this condition, but from the doses given have failed to perceive any good effect. In the after-stages of an *endocarditis*, when the heart is troubled with recent patency of valve, digitalis is a remedy of the very greatest importance, often relieving the symptoms distinctly and very strongly favoring the development of that compensatory hypertrophy in which lies the only hope of the patient. During the exhibition of the digitalis, however, the patient should be closely watched, and any evidence either of overaction of the drug or of overgrowth of the heart should lead to the suspension of the remedy.

In acute *myocarditis* digitalis is commonly absolutely inefficient. How far its action upon the muscle itself will render it harmful is at present unknown.

These statements are so correct that in cases of rapid degeneration of the muscles from diseases of the coronary artery the effect of digitalis can sometimes be made available for diagnostic purposes. When the symptoms point strongly to coronary artery diseases, and digitalis freely given fails to exert any perceptible influence upon the heart, the prognosis is most grave.

Digitalis in large doses is a valuable cardiac stimulant in *syncope* or sudden *collapse* from hemorrhage or other cause. To overcome its slowness of action we have used it hypodermically often with excellent effects. From twenty to thirty minims (1.3–1.8 C.c.) of the tincture should be injected into the arm, and repeated in half an hour if absolutely necessary, or a grain (0.06 Gm.) of digitalin may be substituted. In these conditions, however, *strophanthin* is probably better, because more prompt.

In many cases of general debility or so-called *neurasthenia*, although there may be no disease of the organs especially concerned in the circulation, the latter is exceedingly feeble and, as a consequence, all portions of the system are imperfectly supplied with blood. Under these circumstances preparations of digitalis are very useful as general tonics.

A number of eminent physicians assert that they have obtained excellent results by the use of half an ounce of the tincture of digitalis in the treatment of *delirium tremens*, especially in those cases in which the pulse is very soft and feeble. The evidence of the value and safety of the remedy in such cases is too strong to be overlooked, but does not indicate the possession of narcotic properties by the

drug. The rest and sleep which have followed the administration have probably been the result of the cardiac stimulation and the increased flow of blood to the nerve-centres. Enormous doses of digitalis are tolerated in these cases, probably because the heart has become by long habit very much benumbed to the influence of stimulants. Their use is not, however, entirely free from danger.

Digitalis is a very important remedy in the treatment of poisoning by such substances as muscarine, delphinine, aconite, and the nitrites, which have been proved to be directly antagonistic to it in their action upon the heart.

Dobie reports a case of recovery after the ingestion of an ounce of Fleming's tincture of aconite, apparently due to the hypodermic injection of twenty minims of tincture of digitalis and the exhibition by the mouth of three doses in an hour of a mixture of tincture of digitalis (one drachm each dose), brandy, and ammonia.

Digitalis is often of great value in various acute diseases,\* such as *adynamic pneumonia* and *adynamic fevers*, by maintaining the heart's action. It can have no effect upon the diseases themselves, but may help most opportunely to sustain the heart during a crisis or a period of strain upon it. When in any form of *pneumonia*† the right heart is yielding to the strain of forcing blood through pulmonic capillaries pressed upon and reduced in their aggregate lumen by exudation, digitalis may be of service.

With the idea that digitalis is an active *antipyretic*, it has been prescribed in various acute diseases, sometimes with asserted good results. There seems to be no good physiological basis for the antipyretic use of digitalis; but some clinical evidence in favor of such action is furnished by the records of Wunderlich, according to which from half a drachm to a drachm of digitalis, given in divided dose during three or four days in the second or third week of severe *typhoid fever*, immediately produced a slight fall of temperature in a large proportion of the cases, and sometimes a considerable fall. Far more extensive and complete observations must be made upon a rising, not a falling temperature before any satisfactory conclusion can be reached. At present the antipyretic use of digitalis should be purely tentative. In *puerperal fever* Winkel believes that digitalis does good by its action on the heart, by contracting the arterioles of the uterus, and by lowering temperature.

The property of causing contraction of all unstriped muscular fibres has been attributed to digitalis, but, while the probabilities are certainly such as to invite investigation, we have no definite knowledge upon the subject. Dickenson asserts that it has a powerful action in causing the uterus to contract and to arrest hemorrhage,—in *menorrhagia*, a few minutes after an ounce and a half of the

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\* Consult Hankel (*British and Foreign Medico-Chirurgical Review*, xxxi. 513), Grimshaw (*Dublin Quarterly*, June, 1873), and Anstie (*London Practitioner*, September, 1873).

† According to the experiments of F. Badano (*A. I. B.*) the normal toxicity of blood-serum and of urine diminishes very greatly in pneumonia, but is in large measure restored under the action of digitalis.

infusion is swallowed, severe pains resembling those of the first stage of labor coming on, with a momentary profuse discharge of blood and clots, if there be any present, followed by arrest of the flow for hours. Stadion states that digitalis is capable of temporarily but completely annulling the activity of the sexual organs, and that it may be regarded as a true anaphrodisiac. M. Gaunot makes the same assertion, and advises the use of the drug in *spermatorrhœa*.

**Toxicology.**—In poisoning by digitalis, the first symptom of any severity is generally vomiting of mucus and bile, very violent and very often repeated. At the same time a feeling of heat of the head, disordered vision, and vertigo manifest themselves. The pulse at this time in the horizontal position may be full and strong and slow, but on the patient's rising becomes weak and rapid. The face is pale. The vomiting continuing, profound prostration comes on, and the pulse becomes feeble, small, and irregular, although the beat of the heart may be strong and hard. The eyes are very prominent, the pupils fixed and dilated; \* according to Tardieu, an almost diagnostic symptom is the blue color of the sclerotic. Abundant salivation sometimes occurs. Intense headache and pains in the back or limbs are often complained of. Diarrhœa is very generally present; the urine may be suppressed. The intelligence is often perfect in the midst of profound collapse, but delirium more or less violent finally comes on. Death, usually preceded by stupor or by convulsions, takes place most frequently in one or two days, but has occurred as late as the tenth day and as early as three-quarters of an hour.†

H. O. Hall, in accordance with the previous statements of Doroziiez and other French writers, states that when given only in full medicinal doses digitalis may produce hallucinations and even violent delirium. Such results must, however, be an extremely rare phenomenon.

In the majority of cases of digitalis-poisoning the patient recovers. When this happens, the symptoms gradually ameliorate. Cardiac weakness, and even a *bruit de souffle*, with more or less exophthalmos,‡ are said to have persisted for weeks in some cases. In poisoning by digitalin the symptoms are those of rapid digitalis-poisoning,—violent vomiting, intense cephalalgia, and sometimes rachialgia, irregular, feeble, intermittent pulse, and paroxysms of suffocation.

The minimum fatal dose of digitalis is not known.

A large teaspoonful of the tincture is said to have caused alarming symptoms in a young puerperal woman (Tardieu); twenty grains of the extract proved fatal on the tenth day (Tardieu), and two and a half grammes of the leaves in infusion on the fifth day (Tardieu); fifty granules (one-fiftieth of a grain each?) of digitalin have been recovered from (Tardieu); about one-fourth of a grain of digitalin pro-

\* Hauber (*Münch. Med. Wochensch.*, 1890) details a case of death, due, according to his belief, to digitalis-poisoning, with contraction of the pupils.

† See case reported by M. Barth (quoted by Tardieu). In a case of poisoning by ten grammes of tincture of digitalis, said to contain twenty milligrammes of digitalin, the symptoms were vomiting, great pain in the head, prostration, a very small pulse,—40 per minute,—anuria, and a systolic bruit heard over the whole heart, having its maximum intensity at the base. Recovery occurred in two days (*Mém. Soc. de Méd. de Bordeaux*, 1884, 397).

‡ G. H. M. C., July, 1874.



duced very violent but not lethal symptoms. In the only fatal case of digitalin-poisoning we know of (*Affaire Couty de la Pomerrais*), the amount ingested was unknown. In a case reported by Frank Radcliffe, one-twentieth of a grain of *Nativelle's digitalin* is said to have caused vomiting, profuse sweating, feeble, irregular, intermittent pulse, shallow and slow respirations, coma, ending in recovery.

The treatment—after the evacuation of the stomach and bowels, and the very free administration of tannic acid (as the best, although unreliable, chemical antidote)—should consist in the exhibition of opium, strychnine, and alcoholic stimulants, with rest in the horizontal position. We know of no recorded experiences with the antagonistic poisons to digitalis, such as aconite or muscarine.

E. Zugsmith reports a case of violent cumulative action of digitalis in an infant, in which, acting upon the theory that fever overcomes the cardiac influence of digitalis, he exposed the child to high temperature in a vapor bath at 120° F., with immediate relief of the symptoms. After sixty hours the symptoms had sufficiently disappeared to allow the removal of the child from the bath.

Two cases, one ending fatally, of what may be considered *chronic digitalis-poisoning* have been reported by Köhnhorn. The symptoms were loss of appetite, tinnitus aurium, vertigo, lowering of the rate and force of the pulse, diarrhœa, weakness, general anemia, and syncopal attacks. The only lesion found at the autopsy was congestion with ecchymosis of the gastro-intestinal mucous membrane.

**Administration.**—Digitalis may be given in emergencies where single doses are administered, in much larger quantities than those given as the usual doses. Thus, of the tincture, two fluidrachms or even half a fluidounce may be exhibited; of the infusion, a wine-glassful. Moreover, in desperate cases, the physician is justified in taking the risk of the administration of repeated very large doses of digitalis. We have seen a number of cases of excessively severe chronic cardiac failure, with Cheyne-Stokes respiration, orthopnœa, and almost absolute insomnia, in which the administration of half a fluidrachm or a fluidrachm of the tincture of digitalis three or four times a day has enabled the patient to resume for a time the ordinary duties of life. In almost every case of this character, which we have watched, death has finally come by sudden syncope, while the patient was still going about and enjoying a comfortable life. We do not believe that the arrest of the cardiac action has been due to a direct action of the drug, but to the fact that the enormous doses have stimulated the heart and steadied its expenditure of force, so that it was enabled to go on until the last particle of cardiac vital power was exhausted. H. C. Wood further says that in an experience of forty-four years in which he has used digitalis, frequently in enormous doses, he has seen but one case in which he thought it did serious harm by a toxic action. The infusion of digitalis is believed by many practitioners to be more active than the tincture. This is simply because the infusion is commonly used in much larger doses than the tincture. Either preparation is efficient if properly made from fresh leaves.

When digitalis is administered persistently, its first evident influence may be suddenly developed after long delay. It is said that sometimes the first marked symptom of this so-called "*cumulative action*" is severe syncope, followed by paraplegia, vomiting, diarrhoea, delirium, general insensibility, and death. Such cases must be extremely rare: usually a sudden drop of the pulse is the most serious effect, provided that the *administration of the remedy be at once suspended*. It is a matter of much importance to determine when this cumulative action is to be expected. It is probably connected with slow absorption and elimination, and is much more prone to occur when there is no diuretic effect. It is also very likely to appear after tapping: the sudden removal of pressure from the vessels leads to the picking up from the tissues of serum,—saturated, it may be, with digitalis principles,—and also to the rapid absorption of any digitalis which may be in the alimentary canal.

In a very elaborate, careful research, Fraenkel has found that digitalis glucosides have, when given continuously to the lower animals, a very distinct tendency to cumulative action, and to a sudden passage of the therapeutic over into the toxic effect. The tendency of this influence was much greater with digitoxin than with digitalinum verum; indeed, Fraenkel found it very difficult to experimentally produce marked, continued slowing of the pulse with digitoxin without causing fatal poisoning. For the reason that Heide and also Stokvis have shown that the very soluble helleborein, and because he himself has determined that soluble strophanthin has a marked tendency to cumulative action, Fraenkel believes that this action is due to such permanence of union between the glucosides and the heart tissue that the muscle refuses to give up the glucoside to the process of elimination, and continually adds the new doses to itself.

In the experiments of Fraenkel, digitoxin was found to be an extremely dangerous remedy in the lower animals. It was also made out that 0.08 milligramme was the toxic equivalent of 0.48 of digitalinum verum; so that, as far as physiological experimentation goes, digitalinum verum was found to be much safer and much more prompt in its action than digitoxin.

T. Lauder Brunton and J. Theodore Cash find that high temperature so affects the cardiac inhibitory apparatus in the cat that it will not respond to digitalis, and believe that high temperature greatly interferes with the action of digitalis. In this they are abundantly sustained by general clinical experience; very commonly in high fever it seems almost impossible to obtain the digitalis pulse.\* In *pneumonia* and other diseases with high temperature and a sudden defervescence some care should be exercised in the very bold use of the remedy, lest when the temperature suddenly falls inordinate digitalis effects may appear. Fear of the cumulative action of digitalis should not interfere with its persistent administration in cases of cardiac or other disease in which it is indicated, but should lead the practitioner to interrupt its use at intervals so as to allow

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\* It is probable that all active poisons are greatly influenced by high temperature. It is said that in order to cause the death of dogs suffering from septic fever, fifteen to thirty per cent. beyond the ordinary fatal dose of the following poisons is required: strychnine, curare, morphine, atropine, nicotine, veratrine, digitalin, helleborein, chloral, formaldehyde, sodium nitrite, cobalt, nickel chloride, iron chloride. (See *Arch. di Farmacol. e Terap.*, viii. 1900.)

the clearance of the system. For ordinary cases the official preparations are preferable to *any* so-called "active principle" or secret preparation. Indeed Kakowski failed to obtain the same stimulant effect on the isolated heart, which he obtained from the tincture or infusion, with either digitalein, digitalin or digitoxin.

If a representative of digitalis in small bulk be desired, probably the best preparation is Merck's digitalinum Germanicum.\* This preparation has been deemed uncertain, but according to the clinical reports of Beates and the experiments of Arnold and Wood, this is because it has been habitually given in absurdly small dose. According to the closely agreeing results of these investigators, one-quarter of a grain (0.016 Gm.) is about equivalent to fifteen minims (1 C.c.) of the tincture, and represents the full therapeutic value of digitalis.

Digitoxin, according to the experiments of J. P. Arnold and H. C. Wood, Jr., of Zeltner, and of Curioni, affects the circulation of the lower animals as does digitalis. The tendency of it to act cumulatively, so marked in the experiments made by Fraenkel, has been confirmed by Arnold and H. C. Wood, Jr., and clinically by Zeltner. Digitoxin is locally very irritant, and is probably at least as prone as is digitalis to derange the digestion, although Penzoldt claims that gastric irritation may be evaded by giving the glucoside only when the stomach is full. The dose of digitoxin must at present be considered as unsettled, but one-quarter of a milligramme ( $\frac{1}{250}$  grain) may be used with entire safety.

Zeltner considers that one-quarter of a milligramme ( $\frac{1}{250}$  grain) is equivalent to 0.235 gramme ( $3\frac{1}{2}$  grains) of powdered digitalis; or, in other words, that digitoxin is about one thousand times stronger than the crude drug. Bosse considers one milligramme of digitoxin as equal to one gramme of digitalis (1 to 1000 leaves), and has used the glucoside by enema up to two and one-half milligrammes a day with excellent results. Curioni gives the minimum ordinary single dose as one-half a milligramme ( $\frac{1}{25}$  grain), the maximum as one milligramme.

*Hypodermic Administration.*—When it is desired to use digitalis hypodermically the tincture is the preparation commonly preferred, and in our experience it causes less irritation than do solutions of Merck's digitalin. It is claimed by D. E. Hughes that if the tincture be so prepared as to be free from fatty substances it is hypodermically non-irritant. The hypodermic use of the active principles of digitalis must at present be considered as tentative.

Huchard affirms that by means of gentle warmth an oily solution of Nativelle's digitalin can be made which, when given hypodermically, acts efficiently, and does not cause local irritation,—dose, not to exceed one-sixty-fifth of a grain. It is stated by Madsen, of Copenhagen, that one cubic centimetre (16 minims) of so-called Petit's solution will dissolve one milligramme ( $\frac{1}{64}$  grain) of digitoxin. Of such a liquid four minims ( $\frac{1}{16}$  grain) is the hypodermic dose. *Petit's solution:* Glycerin, 333 parts; alcohol, 95 parts; water to 1000 parts.

\* Local irritation, and even the production of abscesses, have also been noted from "digitalin" by various observers besides ourselves. See Witkowski (*Deutsches Archiv f. Klin. Med.*, xviii. 142); also Pel (*Centralb. f. Med. Wiss.*, 1877, 169).



## APOCYNUM.

*Apocynum cannabinum* or dogbane (also incorrectly known as Canadian hemp) is a milky-juiced herb native to North America, growing to a height of from three to six feet and producing dense cymes of greenish-white flowers. The rhizome, which is the official portion, occurs in pieces varying in length, from one-eighth to one-third inch in diameter, of a greenish color and a bitter nauseous taste.

Schmiedeberg has separated from apocynum two principles, to which he gave the name of *apocynin* and *apocynein*. The latter is a glucoside, while the precise nature of apocynin he did not determine. According to H. C. Wood, Jr., the substance furnished by Merck & Co. under the name of apocynin is inactive.

Fluidextractum Apocyni. . . . . 5 to 15 minims (0.3-1.0 C.c.).

**Local Action.**—Apocynum is so irritant to the alimentary tract that when given in full doses, it acts both as an emetic and cathartic, and has indeed been used clinically for these effects.

**Physiological Action.**—There have been two studies of the physiological action of apocynum, one by Dotschewski and the other by H. C. Wood, Jr. In both these researches it was shown that the drug has an effect on the circulation similar to that of digitalis, causing a marked rise of the blood-pressure with slowing of the pulse, followed, when the dose has been sufficiently large, by a marked increase in the rate of the pulse and a sudden cessation of the heart's action. Both of these investigators agree that the slowing of the pulse does not occur after division of the pneumogastric nerves, and it is therefore probably due to the stimulant effect upon the inhibitory centres. According to Dotschewski the elevation of the blood-pressure is largely dependent upon stimulation of the vaso-motor centres. In the experiments of H. C. Wood, Jr., however, section of the spinal cord did not lessen the power of apocynum to cause an elevation of the blood-pressure, and this observer attributes the elevation of the pressure either to stimulation of the cardiac muscle, or a stimulation of the arterial walls directly, or both. Since both investigators agree that there is a contraction of the vessels of the kidney, it seems probable that there is a stimulant influence directly upon the arterial walls. The character of the pulse-wave after the injection of this drug and the fact that the heart's action is arrested in systolic spasm, as after digitalis, renders it probable that the elevation of the blood-pressure is due to *simultaneous stimulation of the heart and of the vascular system*.

During the stage of rapid pulse electrical irritation of the vagus fails to slow the pulse, indicating that there is probably a late paralysis of the peripheral ends of the inhibitory nerves of the heart.

**Secretion of Urine.**—According to Dotschewski a large dose of apocynum causes such a marked constriction of the kidney vessels in the normal animal as to greatly lessen the flow of urine and may

cause complete arrest of this secretion. When, however, there has been a failure of renal activity brought about through the injection of a depressant drug as chloral, apocynum causes a re-establishment of the urinary secretions.

**Nervous System.**—The action of apocynum upon the nervous system is certainly a very feeble one, since Wood, Jr., found in the frog that after a dose sufficient to cause complete arrest of the heart there is still left some voluntary and reflex power, and that the motor nerve remains irritable for some time after death.

**Therapeutics.**—The original observation of Knapp that apocynum is a valuable diuretic in cases of *dropsy*, especially when dependent upon *hepatic cirrhosis*, has been confirmed by Griscom, Dabney, and many other observers. Lowry has also found the drug of value to aid in the elimination of fluid accumulating as the result of various *cardiac lesions* as well as in chronic *Bright's disease*.

The irritant effect of the drug upon the mucous membranes very seriously interferes with its therapeutic use. According to Griscom, if given in sufficient dose it is both emetic and purgative.

### STROPHANTHUS.

Under the names of Kombé, Inèe, Onaye, and Pahouius poison, there have reached Europe various African arrow-poisons, which are now believed to be derived from one or more species of the tropical genus *Strophanthus*,—apocynaceous climbing shrubs. The name of *Strophanthus Kombé* was given by Sir John Kirk to the tree which he first identified as the source of the Kombé poison; but botanists are at present agreed that the species is the *Strophanthus hispidus* of De Candolle. The seeds, which are the official part of the plant, are one-half to one inch in length, of a greenish-brown color, downy, and characterized by a long awn. They depend for their activity upon the presence of a glucoside *strophanthin*, of which they contain in the neighborhood of two per cent. This principle occurs as a white or faintly yellowish crystalline powder of an intensely bitter taste, freely soluble in water and in dilute alcohol, and sparingly soluble in absolute alcohol.

#### Official Preparations:

Tinctura Strophanthi (10 per cent.)..... 3 to 6 minims (0.2-0.3 C.c.).  
Strophanthinum.....  $\frac{1}{300}$  grain (0.3 Millig.).

**Local Action.**—Locally, strophanthus and strophanthin are exceedingly irritant to mucous membranes. Strophanthin is also an anesthetic, M. E. Gley having found that one-thousandth of a grain of strophanthin caused in the rabbit's eye not only a pronounced myosis but a very rapid and durable anesthesia. It is true that Steinbaugh concluded that this anesthetic action is not due to strophanthin but to some other constituent of strophanthus, but Hare and De Schweinitz have found that in this there was some mistake,

and that strophanthin itself is powerfully anesthetic, but is so irritant that its application to the eye may be followed by inflammation or even ulceration.

*Absorption and Elimination.*—Strophanthus yields its active principle readily to absorption and elimination. It is therefore a promptly acting drug, but has sufficient permanency for the effects of a single dose to last some hours.

**Physiological Action.**—In the healthy man strophanthus in sufficient dose produces fall in the rate of the pulse, with increase of force, without alteration of the respiration, but, if the dose has been large enough, with some gastric irritation and, according to Drasche, a slight fall of temperature. In Drasche's experiments the hypodermic injection of fifteen drops of the tincture induced violent local irritation, repeated vomiting with nausea, pronounced diuresis, and a fall of the pulse. Twenty drops given by the mouth decreased the pulse thirty beats.

In the lower animals strophanthus produces symptoms similar to those that it causes in man, the diarrhœa often being especially violent. No cases of human poisoning have been reported, but after fatal poisoning in the lower animals, evidences of irritation in the gastro-intestinal tract are usually present, and violent irritation and even inflammation of the secreting structure of the kidneys, with small hemorrhages, have been noted by several observers. Mairet and Combemale also state that the blood-globules are frequently altered, and the urine, before death, albuminous. The absence of nervous symptoms until very late in the poisoning shows how very little influence strophanthus has upon the nervous centres. An observation upon the lower animals made by Mayeur and by Lemoine is of great practical interest, especially since similar results have been obtained by some of the German authorities in man. These observers found that strophanthus has a tendency to accumulate in the normal system, so that when small doses are given daily for a length of time, after a time violent and even fatal poisoning results.

The first to make elaborate experiments with strophanthus was T. R. Fraser. One-twentieth of a grain of the extract of the seeds produced, in the frog, stiffness of the limbs and gradual loss of reflexes and of voluntary movements, the respiration continuing after the cessation of the heart's beat.

*Nervous System.*—Upon the general nervous system strophanthus appears to have little or no action. It is true that Bahadurji states that preceding the paralysis there is a stage of hyperesthesia, and that the motor nerve-trunks are affected by the drug, but these affirmations have not, that we are aware of, been confirmed.

*Muscles.*—The chief physiological influence of strophanthus is as a muscle-poison. In Fraser's experiments, the muscles of a leg being protected from the poisoning by tying the arteries, galvanization of the nerve caused active contractions at a time when muscles elsewhere failed to respond to any irritation of their nerves or substance. The first influence of the poison upon the muscular fibre is to increase its tonicity, and when the muscle dies it does not go into relaxation, but passes directly from life into post-mortem rigidity.

*Respiration.*—Both Langgaard and Fraser affirm that the fatal result in poisoning by strophanthus is due to cardiac arrest, but Mairet and Combemale, and also Bahadurji state that at least in



some instances there is a primary arrest of respiration, and, according to Mairet and Combemale, the respiration which is at first hurried is usually distinctly slowed before the fatal termination. There is, however, no sufficient proof that the drug acts upon the respiratory centres, and though asphyxial death does occur, it is in all probability the result of the muscular influence of the poison.

*Circulation.*—The effects of strophanthus upon the circulation are very similar to those produced by digitalis. There is the same slowing of the pulse with usually an increase in the blood-pressure, followed in the toxic dose with a rapid irregular heart and an extremely high pressure. In many cases, however, the blood-pressure does not

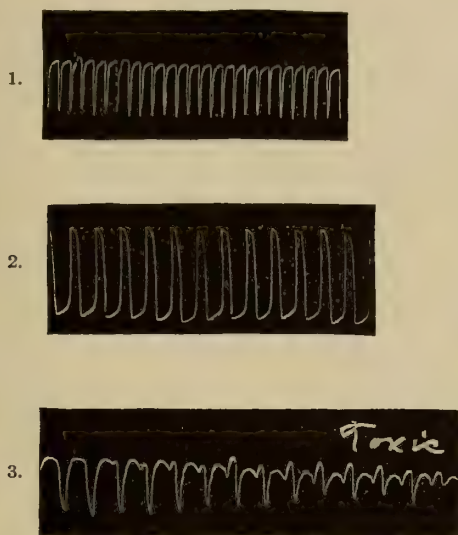


FIG. 13.—SHOWING THE ACTION OF STROPHANTHIN ON THE FROG'S HEART.

1.—Normal. 2.—Therapeutic stage. 3.—Toxic effects.

fall at death with the same suddenness as in digitalis-poisoning, but there appears to be frequently a toxic relaxation of the heart-muscle.

The therapeutic dose of strophanthus affects the heart precisely as does digitalis. There is, however, some reason for believing that the drug acts less powerfully upon the vaso-motor system than does digitalis, although it is certain that the vessels are more or less constricted.

Fraser proved that strophanthin has a direct action upon the heart of the frog, and in this has been confirmed by Bahadurji, by Huchard, by Reusing, by Gley and Lapicque, and other observers. By minute doses the rate of the beat is lessened and the size and force of the aortic pulse-wave increased.

It is noteworthy that Fraser and some other investigators have found that the frog's heart is arrested in systole, while Reusing and Huchard have seen it stop in diastole, and Paul Bert has noted in the cat both systolic and diastolic arrest. The muscle of the frog's heart, according to Fraser, is much more susceptible to the influence of strophanthin than the voluntary muscles, and passes rapidly into post-mortem rigidity, with acid reaction.

The combined testimony of Fraser, of Popper, of Gley, of Paschkis and Zerner, of Langgaard, and other investigators proves that moderate doses of strophanthus cause in mammals pronounced rise in the arterial pressure. As this occurs as well in curarized (Gley) as in normal animals, it must be due to a direct action of the drug, and not secondary to changes in the respiration; after poisonous doses the pressure immediately or secondarily falls gradually to zero. The sphygmographic work of Paschkis and Zerner shows that strophanthus influences the blood-pressure in man as it does in the lower animals.

The general muscular action of the drug would indicate that it has the power of stimulating muscle-fibres in the walls of the arterioles, and Bahadurji asserts that the vessels can be seen to contract under its influence; while Popper found that section of the splanchnic nerve or of the cervical cord does not prevent the rise of the arterial pressure,—a fact which has been confirmed by Gottlieb and Magnus, who further demonstrated with the plethysmograph that there is marked contraction in the size of the spleen evidently due to vascular constriction. In a second research the same observers found the size of the brain was increased rather than decreased by strophanthin, a change which is probably the outcome of the dominant influence of the splanchnic vessels upon the general blood-pressure.

The slowing of the pulse is probably due to the direct action of the drug upon the cardiac ganglia, Paschkis and Zerner\* having found that in the dog it is not prevented by previous section of the vagus; Popper states that in the advanced poisoning there is peripheral paralysis of the vagus without alteration of the irritability of the accelerator nerves.

*Diuretic Action.*—Although several observers have failed to notice an increase in the urinary secretion in man and in animals under the influence of strophanthus, yet the general testimony is too strong to be gainsaid; and it seems established that strophanthus acts not only in cases of cardiac disease but also in healthy men and animals as a powerful diuretic. This indicates that the drug has a direct stimulating influence upon the secreting structure of the kidneys, a conclusion which is confirmed by the renal lesions of the poisoning, and also by the oncometric experiments of Phillips, which showed that strophanthus does not cause vascular congestion of the kidneys.

**SUMMARY.**—Strophanthus is primarily a muscle-poison, whose influence, whatever it may be upon the nervous system, is so subordinate to its action upon the voluntary muscles and upon the circulation as to play little or no rôle in the poisoning. In concentrated form, however, it is paralyzant to the sensory nerves and probably to other portions of the nervous system. The most susceptible portion of the body to its influence is the cardiac muscle, upon which and also probably upon the muscular fibres of the walls of the vessels it acts as it does upon voluntary muscles.

**Therapeutics.**—Strophanthus is used in practical medicine to meet exactly the same indications as those for which digitalis is prescribed. It is, however, less powerful and less certain in its influence for good than is digitalis, but acts more promptly and more fugaciously. Its influence usually begins in half an hour and lasts from four to eight hours. It would seem to be indicated especially

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\* These observers state that sometimes in the normal dog the slow pulse was wanting.

in cases of acute heart-failure, but both its tincture and strophanthin are locally too irritant for hypodermic use except in cases of great emergency. When actively pushed, it probably is no better borne by the stomach than is digitalis; but experience has shown that some individuals are affected unpleasantly more quickly by strophanthus than they are by digitalis, while in others the opposite is the case. In *chronic heart disease* strophanthus stands next to digitalis in the list of useful heart tonics and stimulants, in some cases acting more favorably than digitalis for reasons not apparent, in others extremely useful in combination with digitalis, while in the majority of instances it is chiefly advantageous as a remedy to take the place of digitalis when it is from time to time suspended for the purposes of resting the stomach or preventing cumulative action. Its superiority as a diuretic makes it of especial value in *cardiac dropsy*. When given in overdose it produces burning in the œsophagus and the stomach, with gastric distress and severe vomiting.

M. Furbringer reports three cases in which, after the remedy had been used in a large quantity and for a long time, sudden death from syncope occurred. It may well be that the death was directly caused by the strophanthus, but it is more probably a parallel occurrence to what often happens in advanced cardiac disease treated with very large doses of digitalis.

Zerner and Loaw have employed strophanthus with alleged success in *Basedow's disease* and in *Bright's disease*, and they consider it especially useful in renal affections with secondary failure of the heart, a condition in which we have seen it act most advantageously. Rothziegel and Koralzewski and H. Haas commend it highly, not only in chronic but also in acute Bright's disease.

**Administration.**—The U. S. Pharmacopœia recognizes *Strophanthin* and officially describes it as "a glucoside or mixture of glucosides obtained from *Strophanthus*;" it also assigns to it the dose of one-two-hundredth of a grain (0.3 Mg.). Probably in many cases larger amounts than the official dose are necessary to obtain the desired therapeutic effect. Stahr affirms, as the result of clinical studies with Merck's crystalline strophanthin, that twenty milligrammes, or three-tenths of a grain, may be given in twenty-four hours without producing serious results.

### SUPRARENAL GLANDS.

The suprarenal glands\* are two small bodies located above either kidney in all mammals. For medical purposes they are obtained from the sheep or from the ox. The gland freed from fat, dried and powdered, is recognized by the U. S. Pharmacopœia. It occurs as a yellowish-brown, amorphous powder, with a faint somewhat meaty odor, yielding its activity to, although not completely dissolving in, water.

\* The suprarenal glands have in previous editions of this book been considered among the family of alteratives, but as they are used in medicine almost exclusively for their effects upon the circulation it has been thought much more in consonance with their physiological action and therapeutic uses to class them among the cardiac stimulants.



Glandulæ Suprarenales Siccæ.....3 to 5 grains (0.2-0.3 Gm.).

In 1897 Abel separated a body in the form of benzoyl-chloride from the suprarenal capsules, to which he gave the name of *epinephrin*, and which possessed to a marked degree the characteristic physiological action of the adrenal glands. Subsequently he succeeded in separating the pure base. In 1900 Von Furth separated an active body, to which he gave the name of *suprarenin*, and in 1901 Takamine described a method by which he isolated a principle, to which he gave the name of *adrenalin*.

All of these substances are extremely active stimulants to the circulation, as small a quantity as 0.016 milligramme ( $\frac{1}{40000}$  grain) of adrenalin per kilo injected intravenously being sufficient to markedly elevate the blood-pressure. Abel regards adrenalin as an epinephrin hydrate, since he found that by dehydration, either with mineral acids or by heating in vacuum, adrenalin is converted into epinephrin. He insists on the formula for adrenalin of  $C_{10}H_{13}NO\frac{1}{2}H_2O$  although most authorities agree on  $C_9H_{13}NO_3$ .

The stimulant principle of the suprarenal gland appears to be in the nature of a glandular secretion and has been found by both Dreyer and Ehrmann in the suprarenal vein.

The observation of Pettit, that the adrenals are affected by glandular poisons, as pilocarpine, in the same manner as are the other glands of the body has been contradicted by Ehrmann.

It is certain that the suprarenal glands have other functions besides elaboration of epinephrin, and they probably are concerned with the destruction of poisons, for Audenaysa, Boinet and Abelous have all shown that animals are more susceptible to various poisons after the extirpation of these bodies. Langlois and Charrin discovered that the repeated injection of certain toxins in sublethal doses produced an hypertrophy of the suprarenal glands; but that instead of being physiologically more active, such hypertrophied glands lose their reaction towards ferric chloride and also their effects on the blood-pressure. The fact that the hypertrophied glands affect the circulation less than do the normal is very strong evidence that the circulatory poison is not the same principle as the antitoxic substance.\*

It has long been known that the so-called Addison's disease, which is characterized by a progressive asthenia, a peculiar bronzing of the skin, anemia, and loss of digestive power, with excessive vomiting, results from atrophic or destructive disease of the suprarenal glands, but the immediate cause of the symptoms has never been satisfactorily explained.

*Local Action.*—Locally applied the extract of the suprarenals acts as a powerful constrictor of the blood-vessels. It has of itself no local anesthetic properties, but when used in conjunction with cocaine, enhances the powers of that drug, probably by preventing too rapid absorption (see Meltzer and Auer).

*Elimination.*—The active principle of adrenals is very rapidly destroyed or eliminated in the system, since the effects do not last much over ten or fifteen minutes. Cybulski discovered that the

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\* An interesting confirmation of the fact is the observation of Caussade that the glycerin extract of the suprarenals when injected continuously produces an hypertrophy of the suprarenals precisely as do other toxic bodies; suggesting that the gland destroys its own secretion when in excessive amount.

urine of animals poisoned with suprarenals is capable of producing a rise in the blood-pressure, and therefore believed that the active principle is eliminated by the kidneys. Ott and Harris confirm this fact, but assert that it can be shown only after enormous doses have been given. It would seem, therefore, that only a part of the drug is eliminated by the kidneys. Langlois found that maceration with the liver destroyed the active principle of the gland, that ligation of the hepatic vein prolonged the duration of its effect, and that when injected into the portal vein the suprarenal had comparatively small influence upon the circulation. This last fact has been also noted by Carnot and Joserand, who further determined that injection into the femoral artery likewise destroys the activity of adrenalin. It would seem, therefore, that it is largely oxidized in the liver and muscular tissue. Erhmann believes, however, that adrenalin is neither eliminated nor destroyed, because he finds remaining in the blood after the pressure has fallen to the normal more than sufficient of the principle to act as a circulatory stimulant, and because the blood of such an animal is capable of causing a rise of pressure in another animal.

**Physiological Action.**—The most manifest action of suprarenal bodies is upon the circulation, so that after the exhibition of anything like the therapeutic dose the only symptoms produced are connected with the circulation.

Toxic doses of the extract caused in the frog progressively increasing loss of power without a true paralysis, which seems to be of spinal origin, since Gourfein and Oliver and Schäfer find that after ordinary toxic doses the nerve-trunks and muscles preserve their activity up to death; on the other hand, Vincent asserts that the suprarenal extract is a muscle-poison, producing, when given to the frog in overwhelming doses, a peculiar rigidity similar to that brought about by too much veratrine.

According to Abel and Abbott, epinephrin kills by arrest of the respiration. This paralytic effect upon the respiratory centres is preceded, if the dose has not been too large, by an enormous increase in the rate of the breathing. The lethal dose for a rabbit, according to Abel, is about ten milligrammes.

**Nutrition.**—Although the effect of suprarenal feeding on nutrition seems to be of minor importance, it has been abundantly proven that either the dried capsules or adrenalin is capable of producing glycosuria. This is accompanied with an increased amount of sugar in the blood and apparently disappearance of glycogen from the liver (see Paton).

The injection of the suprarenal extract or its active principle has been shown by a number of observers to produce glycosuria. Croftan found in the suprarenal extract a diastatic ferment which was capable of producing glucose from glycogen, but Hurter and Richards have shown that Takamine's adrenalin does not affect solutions of glycogen, although it causes the occurrence of sugar in the urine. They attribute this effect to an action on the pancreas, since they found degeneration of the islands of Langerhans after adrenalin-poisoning.

Paton determined that adrenalin was capable of causing the formation of sugar from the proteids after the destruction of the carbohydrates of the body; the glycosuria he therefore regarded as a true diabetes.

Drummond has shown that adrenalin is capable of giving rise to acute parenchymatous nephritis.

*Circulation.*—As was first shown in 1895 by Oliver and Schäfer and Szymonowicz and Cybulski, almost simultaneously, after the intravenous injection of the suprarenal extract or its active principle, there occurs an extraordinary rise of the blood-pressure accompanied by a slowing of the pulse. When the blood-pressure has reached its maximum, the pulse becomes rapid. This increase in the blood-pressure, which is of very short duration, is brought about by a simultaneous stimulation of both arterial and cardiac muscles, or else their intrinsic ganglia.

According to Cyon, the late increase in the rate of the pulse is brought about by a heightened excitability of the accelerator centre. Amberg has shown that the slowing of the pulse is not dependent upon a rise of the blood-pressure as is claimed by Gearheart, but is due to a stimulation of the inhibitory centre, being abolished either by section of the vagi or the injection of atropine. The rise of the pressure is not prevented by division of the splanchnics (Cyon) nor of the spinal cord (Oliver and Schäfer). Meltzer and Meltzer and Josué have shown that the division of the sympathetic does not prevent the constriction of the vessels in the ear of the rabbit on the corresponding side. In fact, according to the former investigators, the contraction was more marked on the side whose nervous influences had been destroyed than on the other side. Gottlieb has determined that the vessels of an isolated kidney which had previously been dilated with hydrated chloral were contracted by the suprarenal extract. The pulmonary pressure, according to both Velich and Gearheart, is slightly elevated by the adrenals.

Ott and Harris have found that adrenalin applied externally to the isolated frog's heart produces a temporary decrease of both force and rate followed by an increase in the same, and Gottlieb has found that the isolated mammalian heart is also stimulated by the suprarenal extract. With very large doses the rise of pressure is followed by a gradual fall to the zero point, the heart ceasing in diastole.

In 1903, Josué announced the discovery of aortic arteriosclerosis following the injection of adrenalin. His observations have been repeatedly confirmed by Loeb and Githens and numerous other investigators. These lesions are usually the result of prolonged courses of injection, but Pierce and Bauldauf have observed distinct lesions of the aorta, and also of the heart, following the intravenous injection of a single dose of one minim per kilogramme of 1:1000 solution.

The lesions produced have been limited to the aorta, usually to the arch. They differ markedly in their histological appearances from those seen in the human vascular degenerations, but as pointed out by Adler and Hensell, and also by Pierce and Stanton, these differences are not greater than might be expected when the difference in structure of the arterial walls is borne in mind. The question as to the cause of these lesions appears not yet to have been finally answered. The fact that both nicotine (see Adler and Hensell) and digitalis have been shown capable of producing similar lesions would argue that they were due chiefly to the increased blood-pressure.



On the other hand, Braun asserts that the consentaneous administration of amyl nitrite, which prevents rise of pressure, does not preclude the production of arteriosclerosis by the suprarenal. Pulmonary edema has been reported by Kulbs and others as a secondary result of the use of adrenalin.

**Therapeutics.**—There is at present considerable clinical as well as experimental evidence to show that the extract of the suprarenal capsule is of value in the treatment of *Addison's disease*. It is plain, however, that when the lesion of the adrenals is cancerous or tubercular, supplying artificially to the system an active principle prepared by those bodies cannot affect the progress of the local disease and therefore cannot bring about a cure.

The most important therapeutic use of this drug depends upon its influence upon the blood-vessel walls when locally applied. It is used to counteract the vascular engorgement in the treatment of various inflammations of the mucous membranes, as *rhinitis*, *pharyngitis*, *conjunctivitis* and the like.

According to Königstein and De Schweinitz, the retinal vessels are not affected when the drug is instilled into the eye. It does not dilate the pupil\* nor influence accommodation. It seems to possess the power of penetrating the skin and of whitening the hyperemic skin of *chronic eczema*.

It is difficult to say precisely what value this method of treatment has in acute inflammations. De Schweinitz is of the opinion that, although the application of the suprarenal solutions will produce a blanching of the inflamed part, it does not hasten the cure of the disease, and Kyle has seen cases of acute coryza made decidedly worse by the treatment. In *hay fever* it frequently gives good results, but in many cases fails entirely to relieve the symptoms. On account of its local vaso-constrictor action it is also of use in controlling local hemorrhages, as *epistaxis*, *hematemesis*, enteric hemorrhages in *typhoid fever*. Various authors recommend it for the purpose of preventing hemorrhage during operations on the throat and eye. As pointed out by Kyle, operations done under adrenalin ischemia are likely to be followed by post-operative bleeding. Its effect in constricting the blood-vessels is not likely to make it of any value as a styptic in internal hemorrhages. Carnot and Joserand have shown that if injected intravenously it does not produce visceral hemostasis. Moreover, these authors find that its action as a local styptic differs very markedly in different portions of the body. Thus, when injected in the kidneys, it has no hemostatic action at all; much less power when applied to the intestines or stomach, than in the nose.

Suprarenal extract and its active principle have been suggested, and to a certain extent used, as circulatory stimulants in conditions of sudden circulatory failure, especially in *shock* during operation. The extreme fugaciousness of its action makes it, however, even in

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\* Meltzer, Ott, and Harris assert that after section of the cervical sympathetic it does dilate the pupil.

these acute conditions, of comparatively little value, and the effects of its repeated use in causing arterial degeneration and pulmonary œdema, render its repeated use very dangerous. We have seen patients who, we believe, were being killed by confidence in this drug as a circulatory stimulant. Internally it has been recommended by Cohen for the relief of *asthma* and *hay fever*, and by Floersheim in *endocarditis*, but it is extremely doubtful if it is of value in either of these conditions. Schäfer recommends its employment in *uterine hemorrhages*, as does also Floersheim. The former believes that it controls the hemorrhage by stimulation of the uterine muscle.

**Administration.**—Locally the suprarenal gland may be used in the form of a watery extract of from five to twenty per cent. Adrenalin may be applied in strengths varying from 1 to 1000 to 1 to 10,000, either by atomizer or by tampon. Of the 1 to 1000 solution of adrenalin from five to thirty minims (0.3–2.0 C.c.) may be given hypodermically. In Addison's disease the crude gland is preferable to any of the active principles.

### CONVALLARIA.

The rhizome with the roots of the lily of the valley, *Convallaria majalis*, is recognized by the U. S. Pharmacopœia. It occurs in pieces of indefinite length about an eighth of an inch in diameter and somewhat branched. It has a characteristic odor and a bitterish somewhat acrid taste.

In 1859 G. F. Walz discovered two active substances, *convallarin* and *convallamarin*. Of these, the first is crystalline, insoluble in water, and, according to W. Marmé, when taken in doses of three or four grains, acts as a simple purgative. The glucoside convallamarin is soluble in water, and is the principle to which the plant owes its action upon the circulation.

Fluidextractum Convallariæ.....5 to 15 minims (0.3–1.0 C.c.).

**Physiological Action.**—Marmé found that convallamarin kills by a direct action upon the heart, and in moderate doses first slows and then quickens the pulse; previous division of the vagi did not interfere with the development of these phenomena. Sée finds that in the dog it first slows the action of the heart and increases the blood-pressure decidedly, the respirations at the same time becoming fuller and a little less frequent. If a toxic dose has been given, the heart's beats becomes very rapid and irregular, the arterial pressure still being much above normal; finally the pressure begins to fall, the cardiac pulsations to grow more feeble, and death occurs through syncope. It is stated that the pneumogastric nerves are weakened but never paralyzed, while the general nervous system is not affected. In man the action of the drug upon the circulation is as in the lower animals, and there is said to be usually produced profuse diuresis

and sometimes purging. In Isaew's experiments upon frogs with convallamarin, the heart was arrested in ventricular systole by two milligrammes of the pure convallamarin, the frog continuing to live for a long time, the remedy seemingly having no effect upon its general nervous or muscular system; isolating the heart had no effect upon the action of the poison.

The fact that the heart is arrested in systole by convallamarin has been confirmed in the frog by Coze and Simon, in the dog by I. Ott, and it would appear, therefore, that the drug is a cardiac stimulant, more or less similar to digitalis in its action. Unfortunately, however, Sée affirms that in the dog the heart is arrested in diastole, that organ not being able to respond to the most powerful galvanic stimulant; Leubuscher states that convallamarin causes in the frog systolic cardiac arrest, but diastolic cardiac arrest in the mammal; and further, that in no doses does it in the mammal elevate the arterial pressure; while Leo Löwenthal, using the same preparation in exactly the same manner and dose upon different frogs of the same species, obtained diverse results which he himself was at a loss to explain. The evidence is so contradictory as to suggest that different observers have used different substances under one name. J. Nathanson asserts that the confusion is largely due to the impurity and lack of genuineness in the products used, even Merck himself having admitted that his commercial convallamarin is not the pure principle. Nathanson found that convallarin produced in man, when given in doses of 0.06 to 0.12 gramme three or four times daily, only nausea, diarrhoea, and gastric pain; while convallamarin administered in daily amounts gradually increasing from 0.03 to 0.3 gramme reduced the rate of the pulse and markedly increased the flow of urine, only in very rare cases causing nausea or vomiting.

**Therapeutics.**—The lily of the valley is said to have been long used by the Russian peasantry for the relief of dropsy, and in 1880 Troitzky and Bojojawlewsky called attention to it as a valuable remedy in *cardiac valvular disease*, especially when associated with *dropsy*. Sée recommends it in *palpitation of the heart*, *cardiac dilatation*, *fatty degeneration*, and other forms of cardiac weakness, also in *valvular lesions* with failing heart-power; in a word, in the class of cases in which digitalis is now used. When there is dropsy, its positive diuretic action renders it especially valuable, and in some cases it purges freely, probably through the convallarin. The value of the remedy has been confirmed by H. Desplats and by several other practitioners. Although condemned after trial by B. Stiller, by Pel, by Leyden, by Jacobi and Lubilinski, and by G. Leubuscher, it has been highly praised by Silvestrini and by E. Maragliana. E. Sansom gives as the result of his experience that convallamarin is very useful in *mitral stenosis* with failing of the heart. Marmé found that the fatal dose of convallamarin was, for the dog, 0.015–0.03 gramme; for the cat, 0.005 gramme; for the rabbit, 0.006–0.008 gramme. Sée gives, of an aqueous extract of the whole plant, from fifteen to



twenty-three grains a day; Bojojawlewsky, each day an infusion representing from fifty to one hundred grains of the plant. The results obtained by Nathanson show that great caution must be exercised in the practical use of the active principles of convallaria.

### SPARTEINE.

Sparteine is a liquid alkaloid obtained from the *Cytisus Scoparius*, or common broom plant. (See *SCOPARIUS*.) It is colorless, of a penetrating odor and extremely bitter taste, soluble in alcohol, in ether, and in chloroform. Sparteine sulphate occurs in colorless prismatic crystals or granular powder, freely soluble in water and in alcohol, having a neutral reaction and a bitter, slightly saline taste.\*

Sparteine Sulphas..... $\frac{1}{4}$  to  $\frac{1}{2}$  grain (0.015–0.03 Gm.).

**Physiological Action.**—The ordinary therapeutic dose of sparteine produces no very definite symptoms, but Legris found that in doses of thirty centigrammes or over the alkaloid caused vertigo, headache, palpitations, and formications in the extremities; while Garand noted that forty centigrammes produced decided cardiac pain, with paraplegic paresis, these symptoms appearing about twenty minutes after the injection of the alkaloid, and reaching their maximum in from four to five hours.

In the lower animals sparteine in large doses causes marked nervous disturbances. (See Husemann, Mitchell, Schroff, De Rymon, Griffe, and others.) There appear to be two stages of the poisoning. The first of these is characterized by trembling, incoördination of movements, increase of reflexes, clonic and tonic convulsions, embarrassment of respiration, acceleration of the pulse, and enfeeblement of the heart; the second, by enfeeblement of all the functions, the respiration becoming more and more depressed, and death preceded by convulsions occurring from respiratory paralysis. Fick found that by artificial respiration life may be prolonged for a very considerable period.

**Nervous System.**—The conclusions reached by experimental physiologists in regard to the action of sparteine upon the nervous system are so contradictory as to imply that different alkaloids have been used under one name, one group of observers finding a palsy of central origin and the other concluding that the drug paralyzes the peripheral nerves.

According to Fick and Mitchell, sparteine has a distinct influence upon the cerebrum; and Fick, Gluzinski, and other observers have found that the loss of reflex activity and the fatal arrest of respiration are due to centric paralysis; while De Rymon, Griffe, and Gluzinski are in accord in affirming that neither the motor nor sensory nerves are affected. In this they are confirmed by Cerna, who even states that the local application of strong solutions has no sensible effect upon the nerves. On the other hand, Fick and Mitchell state that the motor nerves are

\* The hydrochlorate of *oxysparteine*, an oxidation product from sparteine, is freely soluble in water, and has been used with asserted good results hypodermically by Von Oefe, in dose of six-tenths of a grain, as an active cardiac stimulant. See K. Hürthle (*Arch. f. Exper. Path. u. Pharm.*, 1892).

attacked, and A. R. Cushny and S. A. Matthews find that sparteine is closely related in its physiological action to conium, its chief influence being upon the peripheral motor nerve-endings in the muscle, whereby it causes a paralytic asphyxia. Guinard and Geley state that sparteine locally applied paralyzes the sensory nerves in the eye, and may even be substituted for cocaine in operations upon the eye.

Muto and Ishizaka conclude that the fatal failure of respiration of sparteine-poisoning is due to the depressing action of the drug upon the peripheral phrenic nerve as well as to an action upon the respiratory centres.

*Circulation.*—Although the subject of the action of sparteine upon the circulation has been investigated by Laborde, Griffe, Garand, Masius, Gluzinski, Cerna, A. R. Cushny and S. A. Matthews, the results reached have been so discordant as to make their reconciliation at present impossible. The chief facts, that seem to us to be fixed, are that a sufficient dose of the alkaloid produces a pronounced fall of the arterial pressure, which is, at least in part, due to a direct action of the drug upon the heart. The more important question, whether the small dose of sparteine is or is not a cardiac stimulant, cannot at this time be finally answered.

The effect of the alkaloid upon the pulse-rate in its fullest serial development appears to be a primary slowing, followed by an acceleration, which in turn gives way to a pronounced decrease below the normal. The size of the dose is a very potent factor in determining the action on the pulse-rate; thus, if a very large dose is given the pulse at once becomes slow and remains slow. Again, the slowing before acceleration of the pulse has not been noted by various observers, and probably occurs only after very small doses, and in some cases, according to the researches of Gluzinski, it is due to a primary excitement of the vagi nerve. Fick, Griffe, Garand, Masius, Gluzinski, and Cushny and Matthews are in accord in stating that the acceleration of the pulse is due to peripheral paralysis of the pneumogastric nerves, with its consequent withdrawal of inhibition, while it seems to be proved that the final slowing of the pulse is the outcome of a direct impulse of the sparteine upon the heart itself. Neither muscarine (Fick) nor atropine (Cushny and Matthews) prevents the action of sparteine upon the heart.

Garand, Gluzinski, Pawlow, and Cerna all affirm as the result of their own experiments that there is a distinct primary stage of increased arterial pressure; and in the experiments of Cushny and Matthews such rise of pressure immediately followed the injection of five milligrammes of the alkaloid into the veins of rabbits and cats, whether they had or had not been paralyzed with curare or other drugs. According to Pawlow, this rise of blood-pressure is due chiefly to stimulation of the vaso-motor centres; while Cerna reached the conclusion that it is caused partly by an increased activity of the heart and partly by centric vaso-motor stimulation. Cerna compares the action of sparteine to that of digitalis. Cushny and Matthews conclude that sparteine is entirely apart from digitalis in that it does not prolong systole, but slows the pulse simply by increasing diastole; and in that it favors excessive dilatation of the heart, and in any dose is a sedative rather than a stimulant to the viscus. They find that in the mammal the rise of blood-pressure is very brief and does not occur when the drug is given by the stomach. They conclude that the rise is not due to any specific influence of the sparteine, but is called forth by local irritation.

*Muscles.*—When applied locally to the muscles, sparteine has some influence in diminishing their excitability and prolonging the duration of the latent period (De Rymon, Griffe, and Gluzinski).

But it does not destroy the functional activity of the muscles, even when brought in direct contact with them in a concentrated form, and its muscular influence is too feeble to be manifested in general poisoning.

*Kidneys.*—It is still doubtful whether sparteine does or does not fully represent the diuretic influence of *scoparius*. Griffe affirms that in his experiments upon rabbits it produced absolute decrease in the excretion of urine, and although some clinicians assert that it acts in a man as a distinct diuretic, others affirm that any increased diuresis is secondary to the regulation of the circulation.

**Therapeutics.**—The use of sparteine in diseases of the heart has been studied by a number of clinicians, notably Sée, Garand, Roland, Voit, J. M. Clarke, Kurloff, and Pawinski, who are all in accord in affirming it to be of value in the treatment of cardiac affections, in which it slows the pulse and renders it more regular, increases diuresis, and is superior to most other cardiac remedies in its power of controlling general nervous excitement. Pawinski states that in pure *nervous palpitation* it exceeds digitalis in power and certainty in action, and that it is a valuable sedative in *hysteria*, *neurasthenia*, and allied conditions. Both Pawinski and Sée assert that it has a remarkable power of regulating the heart's action; the latter observer, indeed, affirms that no known remedy equals it for the purpose of making an irregular pulse regular. On the other hand, Pawinski warns against its use in cases in which the heart-muscle is believed to have undergone degeneration. Its action is a rapid one, the symptoms produced by it, according to Clarke, Sée, and others, developing in thirty minutes to an hour after its ingestion, and continuing for five or six hours. According to Clarke, these symptoms consist primarily of a marked retardation of the pulse, with increase of the force and of the arterial tension, the skin at the same time becoming red and moist, while the respiration, which is at first quickened, soon becomes slower and fuller than normal. In overdoses it is said to cause very high tension of the pulse, with sharp cutting or throbbing pains in the cardiac region, and sometimes nausea. It has been employed with asserted excellent results in all forms of *valvular disease*, in *asthma*, and especially in *functional cardiac* derangements. The very important statement made by Clarke, that it will control the pulse-rate and general symptoms in *Graves's disease*, receives some confirmation in the work of Pawinski and in our own experience. Some clinicians, notably Hans Leo, and Hiero Stoessel, have found sparteine, however, a very uncertain remedy. We do not believe that for general purposes it nearly equals digitalis; in our own trials with it in organic cardiac cases the results have been very unsatisfactory. It may be useful as a succedaneum to digitalis, and even as a substitute in neurotic cases. Pawinski gives 0.016 to 0.04 gramme three times a day, increasing gradually to 0.6 gramme during the twenty-four hours. The statements of Guinard and Geley, that sparteine may be used successfully externally like guaiacol for an



antipyretic, are strongly contradicted by Lannois. The sulphate may be used in pill or solution in commencing dose from one-quarter to one-half a grain (0.016-0.03 Gm.), cautiously increased to two grains (0.13 Gm.) if required, and repeated every six to eight hours.

### ADONIDIN.

*Adonis vernalis*, a plant of Northern Europe and Asia, contains a glucoside to which Cervello has given the name of *adonidin*. According to Cervello, adonidin causes in the frog first increase in the force of the systolic contractions, then irregularity of rhythm with long diastolic pauses, and finally arrest in violent systole, the most characteristic phenomenon being the peristaltic movements which precede the cardiac arrest. According to H. A. Hare, adonidin first increases and then slows the rate of the beat in the cut-out frog's heart, while its injection into the frog is followed by a period of slowing of the cardiac movements, with long diastolic pauses, succeeded by great increase of the pulse-rate, which in turn gives way to slow movement, ending in arrest. The heart, either within or without the body, stops in diastole. Although Cervello and also Guirlet state that the heart is arrested in systole, Hare affirms that, whether the heart be isolated or *in situ*, the arrest is diastolic. The contradiction is not easily explained, unless it be through the observation of Guirlet, that in the rabbit he has seen the left ventricle in permanent systolic contraction, with the other cavities dilated and full of blood. The slowing of the pulse noted by Hare was found by him to be due to stimulation of the pneumogastrics, as it was prevented by their section. That the diastolic arrest was not merely an occasional phenomenon the result of excessive inhibition, as is sometimes seen from digitalis, was proved by its occurring after section of the vagi, as well as by the fact that galvanization of these nerves in the later stages of the poisoning failed to inhibit the heart, the nerves appearing to be paralyzed. According to Kakowski adonidin differs from the other heart tonics in that it produces a dilatation instead of a contraction of the coronary arteries.

In Hare's experiments adonidin increased very distinctly the arterial pressure in the dog, while decreasing the pulse-rate. After large doses the first rise is followed by a marked fall of arterial pressure, with irregularity of the heart's action, and finally diastolic arrest. The experiments of Cervello and of Bubnow are in accord with those of Hare in showing that the drug produces first rise and then fall of pressure. Hare found that in animals whose spinal cord had been previously cut, a rise of pressure followed the exhibition of adonidin, but was not so great as in the normal dog, so that it is possible that the drug acts as a stimulant not only on the heart but also on the vaso-motor system. The first slowing of the pulse, according to Hare, is the result of stimulation of the inhibitory nerves, since it was prevented by their previous section, while the final fall

of pressure is, at least in part, due to the vaso-motor palsy, since neither galvanization of the sciatic nerve nor asphyxia had any effect at a time when the heart had still considerable power.

**Therapeutics.**—In 1879 Adonis vernalis was introduced to the medical world as a cardiac stimulant by Bubnow, a pupil of Botkin. Since then it has been tested by a number of physicians, with fairly concordant results. The general testimony is that its action in disease resembles that of digitalis, and that it is useful in the same class of cases. It is much more prompt than is digitalis, and Durand affirms that it has no cumulative tendency. There has been some difference of opinion in regard to its diuretic action, and whatever of such influence it has must be attributed to its action upon the circulation in the kidneys rather than to any marked direct power over the secreting structure. Durand asserts that it never produces disturbances of the alimentary canal, but Lublinski and Huchard have both seen it produce so much vomiting or diarrhœa as to require its withdrawal. In a case reported by Durand in which by mistake three grains of adonidin were given every half-hour, violent vomiting and diarrhœa were the most troublesome symptoms. Bubnow employed the infusion made from the whole herb four to eight parts in one hundred and eighty parts of water, and of this he administered a tablespoonful every two hours. Durand gives the dose of adonidin as 0.02 centigramme (one-third of a grain) every three or four hours.

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## FAMILY II.—CARDIAC DEPRESSANTS.

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THERE are certain drugs which are used by practitioners to decrease the activity of the circulation, and it is these which are here considered under the heading of *Cardiac Depressants*. Many, in fact all of them, possess other powers besides those which cause them to be considered under this caption, and none of them are in very close accord in these qualities. There is, however, a *general* resemblance in the action of such as are derived from the vegetable kingdom, in that they are all depressants to the motor nervous system and yet all produce convulsions. H. C. Wood has made an especial experimental study of these convulsions, and has found that they are cerebral and not spinal, because they do not occur in any part of the body separated by section of the cord from cerebral influence. Further, they are probably due to disturbance of the circulation at the base of the brain, for the following reasons, the truth of each of which has been experimentally determined: first, lessening of the circulation at the base of the brain will cause convulsions; secondly, the convulsions produced by the cardiac depressants do not occur until the arterial pressure is reduced about one-half; thirdly, if the disturbance of the cerebral circulation be artificially increased by tying the carotids previous to poisoning, or in any other way, the convulsions come on sooner and are more violent; fourthly, in some animals the convulsions caused by arresting circulation at the base of the brain are feeble and ill-defined, while in others they are violent, and in species of the first order cardiac depressants produce but slight convulsions, while in species of the second order they cause violent convulsions.

The indications for the use of a cardiac depressant may be said to be increased arterial tension, sthenic fevers, and severe local inflammations. In order that a rational selection of the various drugs may be made for any individual case, it is necessary to study how, in these various conditions, relief is afforded by an arterial sedative. When there is circulatory excitement from irritation or excitement of the heart, the mode of relief is too obvious to need discussion. It is plain that in such a case a drug should be selected which simply depresses the heart's action and does nothing more. When there is severe inflammation, such as pneumonia, with high arterial tension, the effect desired is a lessening of the flow of blood to the part. A simple cardiac depressant may do this by lowering the force of the circulation, but a vaso-motor depressant is far more powerful. The blood-vessels of the inflamed part are already dilated, and consequently attract blood, as it were, to the part. If the remedy dilates



all the blood-vessels, this local attraction ceases, and blood is diverted from the inflamed tissue. It would appear from the experiments of Ludwig, Schiff, and others that the blood-vessels of the body, after complete dilatation, are able to hold twice their normal amount of blood, and Golz (quoted by Fothergill) found that the intestinal vessels by themselves were able to contain all the blood of the body. These facts show how by means of an arterial sedative, which paralyzes the vaso-motor centres, "we can bleed a man into his own blood-vessels," or, in other words, get much of the effect of a venesection by drawing blood from the diseased part.

### ANTIMONY.

The only salt of antimony which is used to any extent in practical medicine is the antimony and potassium tartrate, or tartar emetic. This occurs in the form of transparent, efflorescent crystals, or as a white, granular powder.

Its taste is at first very slight, but after a time styptic and acrid. In some persons it blisters the tongue and lips after a few moments of contact. Tartar emetic is insoluble in absolute but soluble in dilute alcohol, soluble in from two to three parts of boiling water, and in fifteen and a half parts of water at 77° F. It is incompatible with alkalies and with acids, including tannic acid and substances containing it.

#### Official Preparations :

Antimonii et Potassii Tartratis

[Tartar Emetic].....  $\left\{ \begin{array}{l} \frac{1}{12} \text{ grain (expectorant)} \\ \frac{1}{2} \text{ grain (emetic)} \end{array} \right\}$  (0.005–0.03 Gm.).

Vinum Antimonii (0.4 per cent.)... 15 minims to 1 fluidrachm (1–4 C.c.).

Syrupus Scillæ Compositus (0.2 per cent.).....  $\frac{1}{2}$  to 1 fluidrachm (2–4 C.c.).

*Local Action.*—Locally applied, tartar emetic is an irritant, acting upon some very delicate and susceptible skins in a very short time. In most instances, however, its continuous application for several days is necessary to produce any effect. At first there is simply a redness, accompanied by some burning pain and the eruption of small papules, which shortly become converted into vesicles and then into pustules. These are irregular in shape and size, varying from one-eighth of an inch to an inch and a half in diameter, and are very painful. Sometimes these pustules give rise to small sloughs, but generally, if the application be withdrawn, they simply give origin to superficial ulcers, which readily heal.

*Absorption and Elimination.*—Tartar emetic is very rapidly absorbed in the gastro-intestinal tract, and elimination commences almost at once. The minute dose probably escapes from the system altogether through the kidneys, but the toxic dose is certainly thrown off with the secretions from the whole length of the gastro-intestinal

tract, and probably also escapes with the saliva. Elimination is, however, not complete, so that in cases of fatal poisoning antimony may be found in the various tissues of the body.

Masoin believes that the fixation of the antimony in the tissue begins almost at once, because he found that if he gave to the rabbit the minimum fatal dose of tartar emetic, then bled and practised transfusion either with blood from another rabbit or with normal salt solution, the animal died as quickly as did the animal left to the action of the poison; although when five or six times the minimum fatal dose was given bleeding and transfusion greatly protracted life. Moreover, blood drawn from the animal poisoned with the minimum fatal dose was only slightly toxic.

*Circulation.*—In man and in all mammals any dose of tartar emetic, which is sufficient to affect the circulation, produces a steady fall of the arterial pressure, with a pulse-rate which may be at first slowed but soon becomes more rapid than the normal. The fall of pressure is due chiefly to a debilitating influence on the heart, although there is evidence that the vaso-motor mechanism is also depressed.

In the lower animals all doses of antimony sufficient to cause any apparent effect progressively lower the arterial pressure; the pulse is sometimes at first temporarily accelerated, but usually the slowing of the pulse occurs from the beginning of the poisoning. During this period of slow pulse the diastolic pauses are extremely long and the pulse-waves greatly augmented, it may be to five times their original size. After a time the pulse usually becomes very rapid, the pulse-waves very small, the arterial pressure almost extinguished, and in a few minutes diastolic arrest occurs (Ackermann, Ernst Sentz). In the poisoned frog the cardiac contractions are from the beginning lessened in frequency and force, then become more rapid but extremely irregular, with the auricles pulsating more frequently than the ventricles (Radziejewski, Ackermann, Nöbiling). The peripheral vagi are paralyzed so that the diastolic arrest is not inhibitory (Radziejewski). Antimony paralyzes the isolated frog's heart, destroying the irritability of the muscle (Ackermann); digitalis is stated to produce immediate restoration of function (I. Soloweitschyk).

Antimony is certainly a direct cardiac depressant and paralyzant, but the assertion of Soloweitschyk that galvanization of the vaso-motor centre does not elevate the arterial pressure while the heart is still active, taken together with the fact that the arterial pressure falls while the heart is apparently putting forth its normal force, indicates that the poison also depresses either centrally or peripherally the blood-vessel system.

*Nervous System.*—The occurrence in man of anesthesia during antimonial-poisoning has been overlooked, but has been a marked feature in experimental poisonings. According to Radziejewski, the thermic sense is first paralyzed and later the tactile power. Radziejewski and Soloweitschyk have found that the depression of reflex activity occurs after, as before, section of the cord, and is therefore not due to stimulation of the Setschenow inhibitory centre; also that it is not prevented by tying an artery and cutting off access of the poison to the nerve, and is therefore not peripheral. It consequently must be spinal; and, as both observers noted that in the frog and the rabbit voluntary movements persist after the total abolition of sensibility and reflex activity, antimony must be a paralyzant of the *receptive centres or sensory tract of the spinal cord*.

The motor cord probably shares to a slight extent in the depressing influence. The motor nerves and muscles are said to retain their functional power.

*Temperature.*—The influence of antimony upon the temperature appears not to be very marked when the drug is exhibited in ordinary therapeutic doses. Ackermann affirms that, after doses severe enough to induce violent vomiting, the centric temperature is not lowered, although that of the extremities may fall as much as  $3.5^{\circ}\text{C}$ . After poisonous doses of antimony the decrease is very perceptible.\*

*Abdominal Organs.*—Tartar emetic acts as an irritant upon the whole alimentary mucous membrane. The serous discharges from the stomach and from the bowels may be to a certain degree due to the local irritant influence of the poison, but probably to a much larger degree are the outcome of an attempt to eliminate the drug circulating in the blood.

Brinton proved that when tartar emetic was injected into the vein of an animal it was very freely and rapidly eliminated by the stomach. B. W. Richardson has corroborated this, and has also found that a similar elimination follows the inhalation of antimoniated hydrogen. Radziejewski's theory that the emesis is due solely to a local action of the poison is completely disproved by the experiments of Magendie (confirmed by Brinton), in which vomiting was produced by tartar emetic after the stomach had been removed and a pig's bladder substituted. The vomiting caused by tartar emetic must therefore be, at least in part, of centric origin, but Mosso has proved that the local action of the drug also plays an important rôle in the production of vomiting; finding that when the tartar emetic is given by the mouth, vomiting is caused by smaller quantities and more promptly than when the poison is injected into the veins.

*Respiratory Organs.*—The respiration in poisoning by antimony is very irregular, with all sorts of variations in the rhythm of the act, and is probably centrally depressed.

In the advanced stages the pauses are often very long, and the inspiration and expiration so forced and prolonged that very generally, in animals at least, marginal emphysema and subpleural ecchymoses are found after death. The origin of the respiratory trouble is probably somewhat complex, the chief factor being the direct influence of the drug upon the respiratory nerve-centres, and minor causes the intense venous congestion due to the failure of the circulation and the alteration of the blood itself.

Upon the mucous membrane of the lungs antimony acts directly or indirectly, even in moderate doses, as is shown by clinical experience and by the experiments of Mayerhofer.

*Therapeutics.*—There are three indications to meet which antimony and potassium tartrate is constantly employed. The first of these it fulfils by virtue of its powers as an emetic. The discussion of this may be found in the chapter upon Emetics.

The second purpose for which antimony is used is to *depress arterial excitement*. It is chiefly in *inflammation* that tartar emetic is used

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\* Ackermann found that a fall of only  $1.6^{\circ}\text{C}$ . occurred in rabbits killed in an hour, but in those that lived five hours the depression amounted to  $6.6^{\circ}\text{C}$ .



as an arterial sedative. In combination with more decided diaphoretics it is constantly employed by some surgeons in *gonorrhœa* and in various sthenic inflammatory affections. In *pneumonia* it has been very largely used, forming an essential portion of the old so-called contrastimulant plan of treating that disease. According to the method of Rasori, four or five grains a day were at first given, but rapidly increased to twenty-four or even thirty grains daily. Although by the aid of opiates and careful dilution a species of tolerance was often obtained for these heroic doses, the method has very properly been abandoned by modern therapeutists. Whenever tartar emetic is given in such quantities as markedly to depress the circulation, by the vomiting and purging which it causes, it produces in the patient exhaustion as well as depression. Further, by the continuance of its local influence upon the intestinal tract after the period of depression, it interferes with the digestion of food and consequently with the regaining of power. On the contrary, neither aconite nor veratrum directly exhausts, though they powerfully depress. They are, therefore, always preferable to tartar emetic when in a pneumonia or other disease it is desired to produce a temporary pronounced depression of the circulation. In fact, tartar emetic should never be employed as an active depressant of the circulation.

Owing to its action upon the mucous membrane of the bronchial tubes, in the first stages of *bronchitis* tartar emetic is a valuable remedy. After free secretion has been established, other expectorants are, we think, of more service. It should be used only in sthenic cases, and never, unless in the most minute dose, in children or the aged.

As a *counter-irritant*, tartar emetic is used only when it is desired to produce a slow, persistent, and at the same time very decided impression. For further discussion of its application to disease, see the chapter on Rubefacients.

**Toxicology.**—The symptoms of antimony-poisoning are—nausea, violent vomiting and retching, with marked reduction of the force of the pulse, great muscular relaxation, and a feeling of faintness. At the same time the saliva is generally increased in amount and the skin is bedewed with sweat. The vomiting is violent, repeated, continuously re-excited by the slightest provocation, and is accompanied by burning in the œsophagus and stomach and by colicky pains in the abdomen. The matters vomited are first mucus, then mucus with bile, and finally, in some cases, blood. With the gastric disturbance occurs violent and frequent serous purging, the discharges resembling those of cholera, but becoming in some cases towards the last bloody. Cramps may occur in the extremities, and, in conjunction with the serous purging, have caused the antimonial-poisoning to be mistaken for cholera. The exhaustion is extreme, and deepens into collapse, with thready or imperceptible pulse, pinched, livid countenance, suppressed voice, profuse cold sweats, lowered temperature, and at last death from asthenia, generally preceded by stupor or convulsions: indeed, Taylor reports cases in which wild delirium was

present some hours before death. The urine\* in mild cases is increased in quantity, as it is also in the beginning even in fatal cases, but in such towards the close it is generally scanty and bloody, and even suppressed.

There has been described a form of antimonial-poisoning in which neither vomiting nor purging† occurs, the symptoms being simply intense prostration, cold clammy sweat, a sense of oppression in the chest, with the respiration at first increased, then diminished in frequency and embarrassed; a rapid feeble pulse, after a time becoming slow, intermittent, and irregular; delirium, unconsciousness, tremblings, and clonic and tonic convulsions (Husemann). Tardieu states that in some cases of tartar emetic poisoning a rash, exactly resembling that produced by the external application of the drug, has appeared all over the body on the fourth or fifth day.

The symptoms of antimonial-poisoning so closely resemble those of arsenical-poisoning and of choleraic diarrhoea, that when there is no distinct history, certainty of diagnosis can only be reached by an analysis of the excretions. In any suspected case of poisoning it is the duty of the practitioner to save the urine for chemical examination.

The lesions of gastro-enteritis which are usually found after death from tartar emetic are sometimes not present.‡ The venous system is generally very much engorged, and the viscera are intensely congested. Magendie asserted that in animals poisoned by tartar emetic the lungs are always full of portions apparently hepatized; but Ackermann, in twenty experiments, found only some marginal emphysema and subpleural ecchymoses, with, in one or two cases, spots of atelectasis in the lungs. The assertion of Magendie, therefore, is too sweeping; but it is true that, in a large proportion of fatal cases of antimonial-poisoning, emphysema, pulmonary apoplexy, atelectasis, or other structural lesions of the lungs exist. The blood usually coagulates imperfectly.

Solkowsky, of Moscow, has found that when animals are fed upon antimonic acid (one-half to one gramme daily) or other preparations of the metal for from fourteen to nineteen days, the liver, kidneys, and even the heart undergo fatty degeneration; also that there is a lessening of the amount of glycogen in the liver, and in some cases even a total disappearance of it. This has been confirmed by Grohe and Mosler, who state that in the duchy of Brunswick the peasantry give to the geese, when producing the famous fatty livers, a certain quantity of the white antimony oxide every day.

The minimum fatal dose of tartar emetic is not known. Three-quarters of a grain in a child, and two grains in an adult, have proved fatal, but in the latter case extrinsic circumstances favored the

\* What is said in the text is, we think, correct, although authorities differ on this point. Trouseau (*Traité de Thérapeutique*, 4th ed., i. 619) affirms that it is suppressed; Husemann, that it is never suppressed (*Toxicologie*, 854); Tardieu, that it is scanty. For a case in which it was suppressed, see Taylor's *Medical Jurisprudence*, London, 1873, 309. C. Gäthgens (*Centralbl. f. Med. Wiss.*, 1870, 321) found, in some incomplete experiments, an increase of the elimination of urea after repeated non-toxic doses of antimony.

†Husemann states this. Although vomiting is absent in these cases, purging is generally present. We do not remember to have seen the report of a case in which it was absent.

‡For cases, see *Archives Gén.*, September, 1865.

result (Taylor, an analysis of thirty-seven fatal cases); two hundred grains have been recovered from; also one hundred and seventy grains.\*

The *treatment* of antimonial-poisoning consists in washing out the alimentary canal with large draughts of *tannic acid*,—the best known antidote,—in the free administration of opium by the mouth or rectum, or hypodermically if it cannot be retained, the hypodermic injections of strychnine and digitalis if the circulation fails, and the maintenance of the bodily temperature by external application of heat.

*Chronic Poisoning.*—The symptoms following the criminal repeated administration of small toxic doses of tartar emetic, at intervals, are—nausea, mucous and bilious vomiting, watery purging, often followed by constipation, small frequent pulse, and asthenia, deepening into death from exhaustion.

### VERATRUM.†

The U. S. Pharmacopœia formerly recognized under the name of *Veratrum viride* the rhizomes and roots of that North American plant. Very unfortunately, at the recent Eighth Revision of the Pharmacopœia, *Veratrum viride* was dropped as an official title and *Veratrum* defined as the dried rhizome and roots of *Veratrum viride* and *Veratrum album*.

These two plants, one a native of North America, the other of Europe, are so closely allied that by many botanists they have been thought to be identical, though at present they are by most authorities believed to be distinct. The rhizomes are very similar in appearance and probably contain the same alkaloids and resemble one another very closely in their physiological action (see H. C. Wood and H. C. Wood, Jr.). But similarity is not identity, and both the chemical and toxicological evidence indicates that the European plant is stronger than is the North American, and that the two rhizomes probably differ essentially in the proportionate amounts of the various alkaloids contained in them. A number of cases of fatal poisoning by *Veratrum album* have been recorded; we know of none in the healthful adult from *Veratrum viride*. In the poisoning with *Veratrum album*, violent abdominal pain and diarrhœa are usually present; they are rare in poisoning with *Veratrum viride*. In our opinion, the medical practitioner who wishes to produce a profound influence with *Veratrum viride* should always *order and see that he gets*, not the *veratrum* of the U. S. P., but *veratrum viride*.

Although the chemistry of *veratrum* is still in an unsatisfactory condition, there appear to be several alkaloids in it. Of these the most important are, *jervine*, *rubijervine*, *pseudojervine* and *proto-veratrine*. The last named of these is by far the most toxic and at present appears to be the most important active principle.

It should be noted that *veratrine* is *not* the active principle of *veratrum*, and bears no physiological relation to it. Although some

\* See *N. Y. M. R.*, xxiv. 401.

† *Veratrum* is retained in this chapter as our knowledge of its physiological action is somewhat in a state of chaos. It is probably not, however, in any proper sense of the word to be regarded as a cardiac depressant.



chemists have claimed to have obtained veratrine from veratrum, if present at all it is in such exceedingly small quantity as to play absolutely no part in the physiological action of the drug.

**Official Preparations :**

Fluidextractum Veratri.....	1 to 3 minims (0.06–0.2 C.c.).
Tinctura Veratri (10 per cent.).....	10 to 30 minims (0.6–2.0 C.c.).

*Local Action.*—Veratrum viride is not actively irritant, although there is reason for believing that the vomiting which it causes is partly due to some local influence exerted by it upon the stomach. It yields its active principle very rapidly to absorption; its effects become apparent in fifteen to twenty-five minutes after its ingestion. Concerning its elimination we have no practical knowledge, but its active principle probably escapes through the urine.

*Physiological Action.*—The only effect perceptible in man after the small physiological dose of veratrum viride is a reduction of the force of the pulse. If the dose has been a little larger the pulse frequency also falls very markedly, it may be to 40 or even 30 per minute. The volume of the pulse rises, though the force of it is very slight. The final reduction of the pulse-rate is accompanied by nausea, and at last by vomiting, which becomes after a very large dose exceedingly severe. By exercise this slow, large, soft pulse may be converted into a rapid, very feeble and small pulse. Under any circumstances the rapid pulse develops sooner or later if the dose has been sufficient, and is accompanied by intense muscular weakness and great sweating. Finally, there are a running, almost imperceptible pulse; a cold, clammy skin; intense nausea, and incessant attempts at vomiting, or retching, or hiccough; absolute muscular prostration; faintness; vertigo; loss of vision; and semi-unconsciousness. Various observers also speak of an excruciating precordial pain; but this we have not seen. The intestines are usually not disturbed, but severe purging has been noted.

*Circulation.*—When a small dose of veratrum is introduced into the circulation it produces a remarkable slowing of the pulse with some fall of the blood-pressure. After toxic doses the pulse may become exceedingly rapid and the pressure rise to a point very much above the normal. The fall of the blood-pressure, seen after small doses, appears to be due solely to a slowing of the pulse, as H. C. Wood, Jr., has shown that, after section of the pneumogastric nerves, the pulse-rate is not decreased and the arterial pulse is elevated decidedly. The rise of pressure which occurs under these conditions appears to be due chiefly to a stimulant influence either upon the heart-muscle or the nervous mechanism regulating the heart's action, as it occurs after division of the spinal cord. The slowing of the pulse is due solely to stimulation of the cardio-inhibitory centres. The toxic increase in the pulse-rate appears to be brought about through paralysis of the peripheral endings of the pneumogastric nerve.

In 1870, H. C. Wood made an elaborate study of the alkaloids jervine and veratroidine (rubijervine) in which he showed that jervine was a depressant to the respiratory centres to the respiration, to the vaso-motor centres, and to the heart-muscle; and the effect of the alkaloid upon the circulation is at least equally as well marked as its action upon the central nervous system. With jervine the chief action was a depressant action upon the nerve-centres, especially the respiratory centre. It is, however, also an active stimulant to the cardio-inhibitory centres, but its effect upon the cardiac muscle was comparatively slight, although, when given in extremely large doses, it exercised some depressant influence.

In 1890, Salzburger separated two new alkaloids, one of which, protoveratrine, has been studied by Eden. It produces a primary slowing of the pulse with slight fall of blood-pressure, but the pressure soon rises to a point decidedly above the normal even although the pulse-rate may remain slow. The primary fall of the

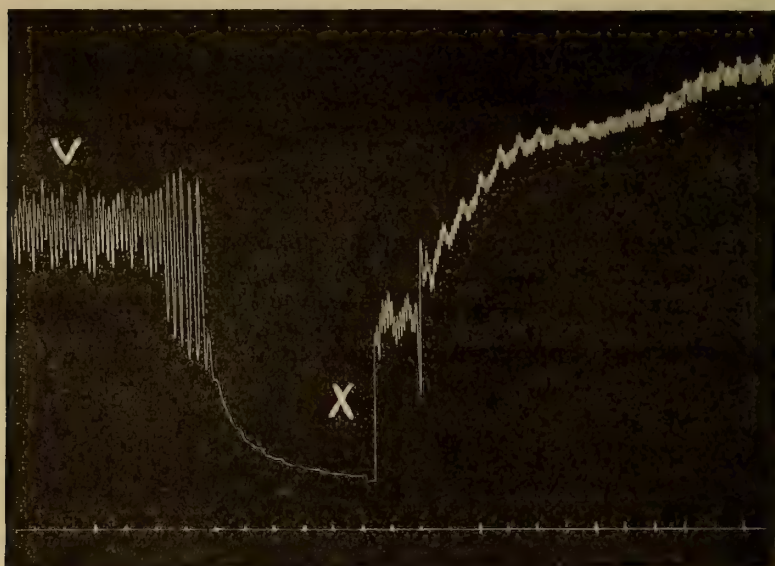


FIG. 14.—THE EFFECT OF VERATRUM ON THE CIRCULATION.

This shows that the fall of pressure caused by Veratrum is due solely to the slowing of the pulse, because the pressure rises above normal after section of the pneumogastric nerves. V—Injection of Veratrum. X—Division of both pneumogastric nerves. Time marker indicates 2 seconds.

pressure appears to be due to slowing of the pulse as it did not occur after division of the vagi. After large doses the pneumogastric nerves may later become paralyzed and there is produced a peculiar dyspnoic type of respiration and frequently convulsions. The rise of the pressure was found to occur also after division of the spinal cord and was therefore largely cardiac in origin.

*Nervous System.*—In the frog, veratrum causes diminution of reflex activity and, in large enough dose, complete paralysis. These changes are probably due to an action on the spinal cord.

**SUMMARY.**—Veratrum is a stimulant to the central cardio-inhibitory mechanism and probably also to the heart muscle, although the slowing of the pulse generally produces a fall of the blood-pressure despite the stimulant influence upon the heart. It is also depressant to the motor side of the spinal cord. In

toxic doses it depresses the respiration, paralyzes the peripheral endings of the pneumogastric nerve and, if given in large enough quantity, finally paralyzes the heart.

**Therapeutics.**—Reasoning from fallacious ideas of its physiological action, veratrum has been, and still is, largely used in the treatment of various sthenic inflammations, as *pneumonia*, *peritonitis* and the like, with the idea that through dilatation of the vessels it would relieve the congestion. As from more recent investigations it would appear that it does not dilate the vessels when given in therapeutic dose, it is obvious that this use of the drug does not find a scientific justification.

Veratrum is also used as a spinal depressant especially in *eclamptic convulsions*. It is recommended that for this purpose it should be given in full dose until the pulse-rate is reduced to about sixty a minute or less.

**Toxicology.**—Overdoses of veratrum provoke vomiting so soon and so certainly that it is somewhat doubtful whether a robust adult could be killed by a single dose of any of its official preparations, especially if prompt and judicious treatment were afforded.

We have several times known a teaspoonful of its fluidextract to be taken, and Percy cites recoveries after the ingestion of a tumblerful of the tincture; after thirty grains of the resinoid; after two doses—a tumblerful each—of a syrup representing a pound of the root to the pint. A feeble child, eighteen months old, was killed by thirty-five drops of the tincture, and a doubtful case of fatal poisoning in the adult is mentioned. J. D. Blake reports a death resulting from the administration of between three and four drops of Norwood's tincture every two hours to a babe eleven months old; and a man convalescing from typhoid fever was killed by a drachm of the fluidextract.\*

In cases of poisoning, vomiting should be encouraged by large draughts of warm water until the stomach is well washed out. Then the patient should be forced to lie flat upon the back, with the head lower than the feet, and the efforts at vomiting should be restrained. If they cannot be checked, and if the prostration be severe, on no account should the patient be allowed to rise up, but must be made to vomit into a towel. A full dose of laudanum should be given by the rectum, and brandy or whisky be administered by the mouth. Tincture of digitalis and strychnine should be given hypodermically. We have noticed that spirits will sometimes be retained only when given undiluted, and in such form will quiet the stomach at once. If the stomach refuses alcohol in any shape, the rectum should be made use of. Ammonia may be employed as an adjuvant to alcohol. External heat is important, and mild flagellations, rubbing with coarse towels, sinapisms, etc., may be used to keep up the external capillary circulation.

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\* Accounts of fatal cases may be found in *Am. J. Pharm.*, 1865; *M. S. Rep.*, xl, 372; and *P. M. T.*, xiv, 863.



## VERATRINE.

This alkaloid is procured from the seeds of *Asagæa officinalis* (*Veratrum Sebadilla*\*). As found in commerce, it is almost always more or less impure, and occurs as a grayish-white powder of an intensely acrid taste, and producing, even in the minutest quantity, when smelled, frequently repeated sneezing, which may continue for hours.

**Official Preparations :**

Veratrina .....	$\frac{1}{30}$ grain (2 Milligm.).
Unguentum Veratrinae (4 per cent.) .....	External use.
Oleatum Veratrinae (2 per cent.) .....	External use.

**Physiological Action.**—Although veratrine is official it has no useful place in practical medicine, and we shall therefore only give a very brief outline of its physiological action. Locally it is intensely irritant to any surface with which it comes in contact, either skin or mucous membrane, and appears to have some local anesthetic effect also. Its most interesting action is its effect upon muscle. It affects the striated muscle tissue in such a way that the contraction following a single electrical shock, instead of relaxing immediately as in the normal condition, may require several seconds for complete relaxation. It appears also to have some depressant influence on both motor and sensory nerves.

The only therapeutic use for which there is the slightest justification, is as a counter-irritant in neuralgia and allied conditions. The drug is actively toxic however, and presents no advantage over other counter-irritant remedies.

## ACONITE.

The *Aconitum Napellus*,† or monkshood, is a tall perennial, indigenous in Europe, and cultivated in this country for the sake of its spike of blue flowers. The leaves are three or four inches in diameter, and cut almost to the base into from three to seven three-lobed, wedge-shaped divisions.

The root, which is the only official portion, is from three to four inches long, very tapering, about three-quarters of an inch in diameter

\* The action of *sabadilline*, the congeneric alkaloid of veratrine, has been partially studied by I. Urpay (*Montpellier Méd.*, 1883, i. 274), who finds it to have only about one-twelfth the toxic power of veratrine.

† All the species of the genus *Aconitum* are more or less poisonous, although *A. Napellus* is the only one official. For a study of the comparative strength of the various aconites, see Schroff (*Journal für Pharmacodynamik*, 1857, 335). He arranges them as follows, commencing with the most virulent: *A. ferox*, *A. napellus*, with its varieties, *neomontanum*, *tauricum*, and *variabile*, *A. cammarum*, *A. paniculatum*, *A. anthora*. The toxic properties of *A. anthora* are very weak. *Lycotonine* is the alkaloid of *A. lycotonum*. For a physiological study of it by Ott, see *Phila. Med. Times*, vi. 25.

*Pseudaconitine*, the alkaloid of *Aconitum ferox*, has been physiologically studied by Boehm and Ewens (*A. E. P. P.*, 1873, i.) and by Cash and Dunstan (*P. Tr. R. S. L.*, Series B., 1902), who are in accord in finding that its physiological action is that of aconitine save only in regard to strength: 0.4 grain of it is said to be equivalent in toxic power to 0.45 of true aconitine. Japaconitine, the alkaloid of Japanese aconite, *Kuzauzu*, *A. japonicum*, and *A. fischeri*, according to Cash and Dunstan, acts physiologically as true aconitine, except that 0.85 grain is equivalent to 0.9 in toxicity.

For local application these three alkaloids may be substituted for aconitine.

at the base. Its taste is bitterish, acrid, and after a little while benumbing, giving origin to intense tingling of the lips and mouth. It may be distinguished from *horseradish root*, with which it has been sometimes fatally confounded, by its external brown color and its lack of odor when scraped. The whole plant is active and tastes like the root. The U. S. Pharmacopœia requires that the root shall contain not less than 0.5 per cent. of aconitine.

In 1833 Geiger and Hesse discovered in aconite the alkaloid *aconitine*. According to the most recent researches, there are in the root, however, besides aconitine, two alkaloids, *benzaconine* and *aconine*, which may also be made by the hydrolysis of aconitine, benzaconine being the *isaconitine*, and the principal constituents of the *napelline* and the *picroaconitine* of older writers (Cash and Dunstan).\*

Aconitine occurs in colorless or whitish, odorless, rhombic tables or prisms. In extremely dilute solution it is capable of producing a characteristic tingling of the tongue or lips, but is so poisonous that it should never be tasted unless in solution of no greater strength than one part in five thousand, and even then with great caution. *Amorphous aconitine* of commerce is a more or less impure mixture, containing decomposition products.

#### Official Preparations:

Fluidextractum Aconiti.....	1 to 2 minims (0.06–0.12 C.c.).
Tinctura Aconiti (10 per cent.).....	5 to 15 minims (0.3–1.0 C.c.).
Aconitina.....	$\frac{1}{100}$ grain (0.16 Milligm.).

**Physiological Action.**—*Local Action.*—Aconite and aconitine are locally irritant, but this irritant influence is soon overwhelmed by the effect of the drug upon the peripheral ends of the sensory nerves, so that numbness and tingling are produced at the point of application. Moreover, the general influence of the drug is so overwhelming that the local effect counts for very little in practical medicine.

*Absorption and Elimination.*—Aconite yields its alkaloids with great rapidity to absorption, and aconitine is capable of passing through the mucous membranes and even the skin, making it, in pure form, a dangerous external remedy. Concerning its elimination we have no knowledge.

*General Action.*—The symptoms which are induced by small therapeutic doses of aconite in man are reduction of the force and frequency of the circulation, a sense of muscular inertia and weakness, and a slight tingling in the extremities or in the lips. If the dose administered is large, all these symptoms are intensified; the muscular weakness is extreme; the tingling is felt all over the body; the pulse

\* The activity of aconite depends chiefly upon the aconitine. According to Cash and Dunstan, *benzaconine* chiefly depresses the motor mechanism within the heart, also depresses the vaso-motor centre, causes slow pulse by vagal stimulation, and is the antagonist of digitalin. *Aconine* is so feeble as to be disregarded in considering the effect of aconite. According to Cash and Dunstan, it has a curare-like action on the motor nerves, stimulates the roots of the vagi, strengthens the ventricular systole, and does not affect the vaso-motor centres.

is feeble, and reduced to 30 or 40 per minute; the respirations are diminished; giddiness and disordered vision may be manifested, especially when the erect posture is assumed. After three or four hours these symptoms gradually subside.

The symptoms produced by aconite in the lower animals are similar to those caused by it in man, the prominent manifestations being great disturbance of the respiration, muscular weakness, vascular depression, and finally death, with or without convulsions. As we have seen the rabbit after the injection of one-sixth or one-quarter grain of Morson's pure aconitine, the animal commences to jump vertically in a very peculiar manner, and often to squeal piteously. The jumping soon grows less and less powerful, and finally is replaced by severe convulsions, during which the animal often lies prostrate on its side. In the dog, however, the muscles have remained without a quiver during all stages of the poisoning; in the horse Harley has noticed convulsions. The convulsions are an inconstant symptom, dependent upon peculiarities of the individual or species, as well as upon the amount injected. Dilatation of the pupil frequently occurs, if it be not, indeed, a constant phenomenon. There is often severe vomiting. Death usually results from asphyxia, but if a large dose be given hypodermically, may occur in less than a minute, probably from sudden paralysis of the heart-muscle.

*Nervous System.*—The mental condition in aconite-poisoning shows that the drug has no influence upon those portions of the cerebrum which are connected with consciousness and intellectuality.

In the frog it abolishes reflex activity by paralyzing the peripheral sensory nerves. After larger doses there is probably also a depression of the motor side of the spinal cord.

The persistence of voluntary movement after abolition of reflex actions, which was first noted by Boehm and Wartmann, and afterwards by Liégeois and Hottot, as well as by Mackenzie, proves that at a certain stage of the poisoning, while the motor pathway from the brain along the anterior columns and the efferent nerves is open, either the sensory nerves or the receptive centres of the cord are paralyzed.

The discovery of Liégeois and Hottot—namely, that in the frog poisoned simultaneously with aconite and strychnine there is a certain stage when no amount of irritation of the nerve will induce convulsion, while a slight direct irritation of the cord will cause violent strychnic spasms—seems to prove that at least the earliest abolition of the reflex activity is due to paralysis of the afferent nerve-fibres. In accord with this, Mackenzie found that when a nerve is protected from the poison by tying its supplying artery, irritation of it causes reflex actions when the remainder of the frog's periphery is insensible; that there is a stage of poisoning in which irritation of the extreme peripheral nerves fails to induce reflex movements, although such movements are called out by irritation of the sensory nerve-trunk; and that in the last stages of the poisoning irritation of the trunk is powerless, while irritation of the posterior columns of the cord still produces wide-spread movements.

In regard to the action of the drug upon the motor nerves the evidence is somewhat contradictory. According to Achscharumow, when a frog is poisoned after the abdominal aorta has been tied, reflex and voluntary activity is preserved in the hind legs long after it has been lost in the anterior portion of the body; and, at the same time, while the brachial nerves, as tested by galvanic stimulation, have lost their power of transmitting impulses, the protected ischiatic nerves have preserved their functional ability. P. C. Plugge confirms these statements, and also affirms that it is especially the peripheral ends of the motor nerves which are affected, since when in the frog's leg the lower portion had been protected from the poison, galvanization of the nerve-trunk a considerable distance above the point of protection caused response in the tributary muscles.



These allegations would seem to prove that aconitine paralyzes the peripheral motor nerves, but are directly contradicted by Boehm and Wartmann, by Liégeois and Hottot, by Mackenzie and by A. Guillaud, who affirm that the nerves and muscles in poisoned animals preserve almost entirely their normal excitability until death, and that shutting off access of the poison to the limb by tying does not affect the development of motor paralysis under the action of aconite.

The explanation of this conflict of testimony is not to be found, as has been suggested by C. Ewers, in the use of different species of frogs, because Plugge employed various species; nor is it in the employment of different commercial aconitines, because Plugge experimented with all the varieties, and found them to vary in power, but not in quality of action. Those observers who have found least influence upon the motor nerves acknowledge some *slight* effect, and that when aconitine is brought in contact with an exposed nerve it rapidly destroys its functional activity; also that after death in the aconitized frog the motor nerves lose their irritability more rapidly than normal (Liégeois and Hottot, Guillaud, S. Ringer and H. Murrell, Laborde and Duquesnel).

From the evidence which has been thus epitomized it seems to us that the most probable conclusion is that aconite exerts a *feeble depressing influence upon the motor nerves*.

*Spinal Cord.*—Our knowledge of the action of aconite and its alkaloids upon the spinal cord is not complete; Boehm and Wartmann, Guillaud, Mackenzie, and Cash and Dunstan believe that after minute doses of aconitine there is, primarily, excitement or stimulation of the motor centres of the cord; Mackenzie affirms that the convulsions which are so severe in the frog after small quantities of aconite are chiefly of spinal origin, though he believes that the peripheral motor apparatus shares the motor stimulation. If the primary stimulation of the cord really occurs in mammals, it must be completely masked; at least we found in a series of experiments that when the spinal cord was cut in the mammal it was not possible to produce aconitic convulsions in those portions of the body separated from cerebral influence, and no evidences of spinal excitement are ever seen in human poisoning. The conclusion of Boehm and Wartmann, that in the later stages of the poisoning there is depression of the motor side of the spinal cord, is probably correct, but so far as we know has never been actually proved. The preservation of voluntary movements in the poisoned frog after the abolition of sensation and of the reflexes shows that the motor paths from the brain to the cord through the muscle are preserved at the time when the afferent apparatus is completely paralyzed, and that the action of aconite on the motor spinal cord is entirely subservient to its influence on the peripheral nerves.

*Muscles.*—The early evidence in regard to the action of aconite upon the muscles was entirely contradictory, Wieland, Bucheim, and Eisenmenger affirming that the muscle-curve is much affected by the drug, Murray and Boehm and Wartmann that it remains unaffected. The researches of Cash and Dunstan seem, however, to prove that aconitine does not increase the irritability of the muscle-fibre, nor when given in moderate doses affect its capacity for work, though in some way it predisposes the muscle to asynchronism in the contraction of its bundles of fibres.

*Respiration.*—Cash and Dunstan, having noticed primary increase of the rate of the respiration by aconitine, believe that the alkaloid acts primarily as a centric respiratory stimulant; but until it has been definitely proved that the amount of air forced in and out of the lungs is increased by aconitine, it must remain doubtful whether it ever has any true stimulant effect. When the poisoning is advanced the respirations in the mammal are slow, with a prolonged expiration

following immediately upon the inspiration. After the expiration there is a long pause, so that the whole breathing-cycle resembles very much that occurring after section of the vagi. The known influence of aconite upon the peripheral afferent nerves in general suggests that the poison disturbs respiration by paralyzing the peripheral afferent fibres of the vagi, but Mackenzie states that in the aconitized animal section of the vagi produces no effect on the respiration; and Boehm and Wartmann affirm that aconite produces its usual effect after division of the vagi. It is plain that even if the aconite does paralyze the peripheral afferent vagi it must also act upon the respiratory centres, since arrest of respiration could not be caused by afferent palsy. As the arrest occurs in the frog before the motor nerves are affected by the poison, Liégeois and Hottot believe that the disturbance is centric; and we think there can be no doubt that *aconite is a direct depressant and paralyzant of the respiratory centres.*

*Circulation.*—The effects of aconite on the circulation are complex and the changes produced by toxic doses not clearly understood. It produces first a slowing of the pulse with a fall in the blood-pressure. The slowing of the pulse is due chiefly to stimulation of the cardio-inhibitory centres, although there is some evidence that the drug affects also the peripheral endings of the pneumogastric nerve. The fall of pressure seems to be due entirely to the changes in the heart, there being a direct depressant action upon the cardiac muscle. The vaso-motor system does not seem to be affected by therapeutic doses.

After toxic doses the pulse becomes more rapid than normal—probably through paralysis of inhibition perhaps from a direct action on the heart itself. Later the rhythm of the heart is seriously affected, the contractions of both auricle and ventricle being very unequal, and the normal auricular and ventricular rhythm seriously impaired (see S. A. Matthews, also J. T. Cash and W. R. Dunstan). The intra-ventricular pressure also varies greatly, and the whole action of the heart is in such a state of confusion as most seriously to interfere with the coronary supply and the general mechanism of the circulation. After death the cardiac muscle fails to respond to galvanic irritation.\*

In some experiments a brief rise of pressure has preceded the fall (Boehm and Wartmann, Laborde, Duquesnel). It is probable, however, that this rise of pressure is secondary, and not directly caused by the poison. Very early the blood-pressure begins to fall; after a time the fall becomes pronounced, and the pulse, which has been at first slowed, grows rapid. Then what is known by some observers as the characteristic condition develops, consisting especially of great and rapid fluctuations of pressure, which may in the dog amount to fifty millimetres of mercury, and may for the moment even carry the pressure to a higher than the normal point. The pulse finally becomes extremely rapid and irregular; the heart is in a condition of delirium, and soon stops in diastole.

In endeavoring to elucidate the cause of the cardiac phenomena of aconite-poisoning it is evident in the first place, that aconite affects the heart directly.

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\* According to S. A. Matthews, during the period of delirium of the ventricle the auricle can generally be restored to regular contraction by cutting one of the big veins and allowing it to free itself of the contents.

Achscharumow affirms that aconitine acts upon the frog's heart, removed from the body, as it does upon the heart of the normal batrachian. Liégeois and Hottot have produced the ordinary cardiac phenomena of aconite-poisoning by placing the alkaloid upon the heart.

The first question that offers itself is as to the cause of the primary slow pulse.

The concordance of recent investigators warrants the conclusion that aconite primarily slows the heart by stimulating inhibition; the stimulation being chiefly centric, but, if the experiments of Matthews be correct, also in a measure peripheral.

Boehm and Wartmann affirm that the development of the slow pulse is not prevented by the previous section of the vagi or by atropinization. Achscharumow, however, states that section of the vagi performed during the early stage of aconite-poisoning is followed by a pronounced immediate rise both in the number of the cardiac pulsations and in the arterial pressure. Lewin affirms the correctness of this, but states that the rise is of very brief duration, and is soon followed by the usual reduction. S. A. Matthews states, however, that after section of the vagi aconite reduces the heart's rate to a slight extent only, and that even this reduction is entirely prevented by the administration of atropine. Cash and Dunstan affirm that section of the vagi in the period of slow pulse from aconite is followed by an immediate increase of the rapidity of the beat.

The rapid pulse of the advanced stages of aconite-poisoning is attributed by S. A. Matthews chiefly to the ever-increasing irritability of the cardiac muscle under the action of aconitine, and to us seems to be in part due to the action of the alkaloids upon the heart-muscle, and to be also in part the outcome of depression of the peripheral vagi.

The evidence given by different experimenters in regard to the condition of the peripheral vagi in aconite-poisoning is somewhat contradictory. Boehm and Wartmann, and Plugge, affirm the existence of vagal paralysis. S. A. Matthews says that "the peripheral inhibitory mechanism is not paralyzed by the aconitine during the irregular stage, as is generally stated;" but we have no doubt as to the accuracy of the assertion of Cash and Dunstan, that, although when the dose of aconitine has been so large as to be rapidly lethal the vagal terminations may not be completely paralyzed up to death, when small lethal doses have been used, complete peripheral vagal paralysis may develop, or a condition appear, also noted by Boehm, in which the vagi may respond one minute to stimulation and refuse to respond the next.

Our knowledge of the action of aconitine upon the vaso-motor system is not complete. The paralysis of the afferent nerves in advanced aconite-poisoning, by shutting off from the vaso-motor centre the impulses which normally reach it from without, must certainly affect the general tone of the vessels, a reasoning which finds strong confirmation in the fact asserted by Boehm and Wartmann, that there is a stage in aconite-poisoning in which galvanization of a sensitive nerve does not produce rise of the arterial pressure, which, however, is developed at once when the vaso-motor centres in the medulla are stimulated.

S. A. Matthews and Cash and Dunstan affirm that the first action of the drug upon the vaso-motor centre is as a stimulant, but we have not been able to find in their papers any sufficient proof of this, and do not believe that the conclusion is probable. It is likely that in the advanced stages of the poisoning the vaso-motor centre is depressed or paralyzed, though this has not been positively proved. The best evidence is that furnished by Cash and Dunstan,—namely, that there is a period in which mechanical asphyxia ceases to elevate the pressure.

That the efferent vaso-motor apparatus is not paralyzed is shown by the facts that in advanced poisoning galvanization of the sympathetics in the neck causes contraction of the vessels (Nunneley), and that the splanchnics retain almost to the last their functional activity.

*Temperature.*—In the very beginning of aconite-poisoning the bodily temperature may rise slightly, but in severe poisoning a very pronounced fall occurs. The reduction of the bodily heat is probably



caused by an increase of heat-dissipation. If vaso-motor paralysis occurs in aconite-poisoning it will account for this loss of heat. Further, it is entirely possible that aconite, without producing vaso-motor paralysis, may, by destroying the conducting power of the afferent nerves, put an end to the automatic relation between heat-production and heat-dissipation. In accord with this is the observation of Brunton and Cash, that in animals exposed to a high temperature, aconite, far from depressing the temperature, favors its increase, while when the animal is exposed to cold, aconite accelerates the fall of the bodily heat remarkably (confirmed by Cash and Dunstan).

**SUMMARY.**—Locally, aconite is slightly irritant at first and subsequently paralyzant especially to the sensory nerves. It yields its active principle rapidly to absorption. Aconite has little direct action upon the cerebrum, unless it be upon the perceptive centres of general sensibility, concerning which there is still dispute. It is asserted by some authorities that the small dose stimulates respiration, but this has not been proved. In toxic dose it acts as a powerful depressant to the respiratory centres, and usually kills by centric paralytic arrest of respiration. It also paralyzes the peripheral fibres of the vagus in the lungs, and thereby notably affects respiratory rhythm. Its action upon the spinal cord remains uncertain, some authorities believing that it primarily stimulates the motor side of the cord, and very late in the poisoning causes centric motor depression. Its dominant influence, so far as the nervous system is concerned, is, however, upon the sensory nerves, affecting primarily their peripheral filaments and involving later their trunks. It has also some, but a much less powerful, depressive action upon the motor nerves. According to some authorities, the stage of nerve-paralysis is preceded by one of nerve-stimulation, but this is extremely doubtful.

Aconite reduces very markedly the rate of the pulse and the arterial pressure, the primary stage of slow pulse being followed by one of rapid irregular pulse, with very fluctuating but still low pressure. The chief cause of the slow pulse is stimulation of the vagal nerve (aconitine, benzaconine), which is followed, when the rapid pulse comes on, by depression of the peripheral vagi. The rapid pulse is in part due to the withdrawal of inhibition, and probably also in part to a direct action of aconitine upon the muscle-irritability. Aconitine appears primarily not to affect the muscular strength of the heart, but on account of the depressing influence of the benzaconine upon the muscle the cardiac force is weakened by aconite from the beginning.

The action of the drug upon the vaso-motor system is not established; several recent observers affirm that the first action of the drug upon the vaso-motor centre is stimulation, which seems to us to be unproved and improbable; in the advanced stages of the poisoning the vaso-motor centre is probably depressed or paralyzed, but even concerning this our knowledge is uncertain. The efferent vaso-motor nerves are not affected.

The bodily temperature is reduced by aconite by an increase of heat-dissipation, and perhaps also by an action on the thermogenetic nervous system. On the glandular system of the body, except that of the skin, aconite has little or no influence.

**Therapeutics.**—The general indication for the use of aconite is to lower arterial action, but the selection of this drug among other cardiac depressants for this purpose should be governed by certain definite principles, depending upon the known peculiarities of its action. When the high arterial pressure is chiefly cardiac in origin, it is the best drug of its class, having in therapeutic dose little or no influence upon the system other than upon the heart, and producing no disturbance of gastric or intestinal digestion. No cases, or reports of cases, of cumulative effects parallel to those caused by digitalis have come under our notice, but when small doses are given continuously there is a progressive increase of effect. In cases of *cardiac hypertrophy*, or when there is in valvular disease excessive compensation, aconite is the best remedy that we have. Given in doses of the tincture, from two to five minims (0.12–0.3 C.c.) three times a day, it acts steadily and persistently. When the administration is free, the effect should always be watched carefully and the dose lessened *pro re nata*.

On the other hand, when a sudden, very powerful influence to meet an emergency is desired, and especially when it is necessary if possible to produce wide-spread vaso-motor weakness and consequent relaxation of the blood-vessels, aconite should not be employed. The overdose is more likely to produce serious results than is the overdose of veratrum.

In *irritative fevers*, as the *ephemera* of childhood from gastrointestinal irritation or other cause, aconite in moderate dose often acts most happily. Especially is it useful in combination with other drugs which have a tendency to increase the secretion from the skin, when it is desired to produce free sweating. If only a moderate but continuous skin effect is desired, aconite may be given with the solution of potassium citrate; to it may be added, if circumstances favor, antipyrine. When it is desired, as in acute *muscular rheumatism* or in a forming *grippe*, to produce very free sweating, a combination of aconite, pilocarpine, and antipyrine is very effective. In *urethral fever* due to the passage of the catheter or bougie, aconite often acts most happily.

A second indication which aconite might be used to fulfil is to *allay spasm*. As, however, its influence upon the motor centres and nerves is much less than upon the sensitive centres and nerves and upon the heart, the indication is better met by other remedies.

A third indication, which it would seem from its known physiological action that aconite should meet, is to *relieve over-excitation of the sensitive nerves*. Although aconite was formerly very much used for the relief of pains which were called *neuralgic*, and is sometimes useful when an acute *neuritis* has followed exposure to cold, and is of a rheumatic type, it is rarely of real service even as a local remedy, and is of no value whatsoever in such diseases as *migraine* when the pain is of centric origin.

Given in full doses in the reflex *vomiting of pregnancy*, aconite is often advantageous, acting probably by benumbing the sensory reflex centres, or possibly the afferent peripheral gastric nerves. We have noticed that relief lasts only so long as decided constitutional effects from the drug are apparent.

**Toxicology.**—When a poisonous dose of aconite has been ingested, the first thing noticed in most cases is a burning or tingling in the throat or in the extremities, soon spreading over the whole body. The pulse rapidly falls in frequency, and in a very little time becomes exceedingly weak, intermittent, irregular, and finally imperceptible; the muscular strength is greatly reduced and sometimes almost entirely gone; the respirations are shallow, feeble, irregular, and infrequent; the general sensibility is very much benumbed, so that marked anesthesia of the surface is present; the skin is bedewed with cold sweat; the countenance is anxious, sunken, livid, and the eyes are often protruded, or are even spoken of as glaring; the pupil is generally dilated, but when there are no convulsions may be contracted; gastric burning is sometimes complained of, and severe vomiting may be present, but the stomach is not rarely retentive. The intellect generally remains unaffected until very near the close, sometimes to the very moment of death. In the collapse of the latter stages of aconite-poisoning the special senses may be lost, especially the sight. The voice is very generally extinguished. Convulsions occur in some cases, not in others; and certainly in some instances, if not always, the patient is unconscious during their continuance. Diplopia, or other disorder of vision, has been noted in some cases. Death may occur suddenly, especially *directly after some exertion* on the part of the patient, from syncope.

The symptoms usually come on in a very few minutes. In the shortest case we have met with, death occurred in thirty minutes. The average time (Reichert) is three and a third hours, the longest recorded case being five and a half hours. Five grains of an extract and eighty minims of a tincture are said to have caused death (Reichert).

The *aconitines* of commerce vary inordinately in strength, so that while one-sixteenth of a grain (prepared by Petit,\* of Paris) caused the death of Carl Meyer in five hours, and a quarter of a milligramme is said to have produced violent poisoning, several grains of the impure article so largely sold have been recovered from. The symptoms have been in general those of aconite-poisoning, but excessively violent pains and convulsions have been very marked features of some of the cases. (For discussion of aconitine-poisoning, see Thomas Stevenson, M. Jules Bassott, also six cases, Lhôte and Vibert.)

The only diagnostic symptom of aconite-poisoning is the peculiar tingling, which is probably always present, though in suicidal cases the

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\* The best discussions of the relative strength of these alkaloids that we know of may be found in *Schmidt's Jahrb.*, cii. 124, and in *Des Aconits*, by J. V. Laborde and H. Duquesnel, Paris, 1883. Lhôte and Vibert (*Annal. d'Hyg. Publ.*, 1892, xxviii.) assert that the crystallized aconitine of Duquesnel is an essentially different poison from the amorphous aconitine of commerce or from the aconitine sulphate of Merck. The latter in the isolated frog's heart they found to produce gradual progressive enfeeblement, while the Duquesnel aconitine caused primarily great increase in the size of the cardiac pulsation, with periods of ataxia, followed by depression.



patient may refuse to reveal it, or in advanced poisoning unconsciousness may prevent its being told. The presence in any case known to be one of poisoning of absolute prostration with almost complete failure of the pulse, great muscular relaxation, and other symptoms of collapse, without vomiting, purging, or any disorder of the pupil or other toxic manifestations, is sufficient for a working diagnosis.

The first indication for *treatment* in aconite-poisoning is evacuation of the stomach; as emetics usually fail, on account of the local gastric anesthesia, the stomach-pump may often be used, but the danger of causing fatal collapse in extreme cases must not be overlooked. Tannic acid may be administered as an imperfect antidote. Hot concentrated alcoholic stimulants should be freely given; strychnine, atropine, and digitalis\* should be used hypodermically with great boldness, tempered with caution. Ammonia may be injected into the veins, if it be found practicable. The patient must be kept upon the back, with the feet a little higher than the head, and external heat be used freely to maintain temperature. Laborde and Duquesnel affirm that in the lower animals death after a usually fatal dose of aconitine can be prevented by artificial respiration; and in a case of human poisoning, if the heart's action were at all sustained, and the respiration failing, Sylvester's method or forced artificial respiration might be resorted to.

### HYDROCYANIC ACID.

Pure hydrocyanic acid† or prussic acid (HCN) is a colorless, transparent, volatile, inflammable liquid, giving rise to giddiness and headache when smelled, and having, it is said, a burning, bitter taste. So poisonous is it that when inhaled it causes death, and it must be handled with the greatest caution: smelling and tasting it are excessively dangerous proceedings. It is, indeed, an imperative rule that no one should experiment with anhydrous prussic acid alone, or under any circumstances in summer, or in a warm room, or in an apartment whose open windows and doors do not admit of a free draught of air. The chemist Scheele, the discoverer of prussic acid, is believed to have been killed by the inhalation of the fumes of this material, whose poisonous properties were first pointed out by the Berlin apothecary Schrader in 1803. The anhydrous acid is soluble in water and in alcohol, but is never kept in the shops, and is not official.

\* The original discovery of J. Milner Fothergill (*Digitalis*, London, 1871, 6), that digitalis is the cardiac antagonist of aconite, has been abundantly confirmed. The careful work of Matthews and of Cash and Dunstan has demonstrated that it is benzaconine which is especially antagonized by the digitalis, atropine being the cardiac antagonist of aconitine. Clinical experience, although still limited in extent, strongly corroborates the experimental evidence of the value of digitalis. Successful cases may be found in *Brit. Med. Journ.*, Dec. 11, 1872 (f3i Fleming's tincture, Tinct. digitalis Mx hypodermically); *Bost. Med. and Surg. Journ.*, Oct. 1879, 544 (f5iii Tinct. aconit. rad., Tinct. digitalis Mlx hypodermically); *Indian Med. Gaz.*, xvii. 323 (Aconitum ferox root forty-eight grains, Tinct. digitalis Mxxv hypodermically and f5i by mouth); *Phila. Med. Times*, xiii. 328. Ammonia injections were unsuccessful in a case reported in the *Australian Med. Journ.*, 1879, i. 283. G. H. Tuttle (*Boston Med. and Surg. Journ.*, 1891, cxxv.) has reported recovery after seven and a half drachms of the tincture, under the free hypodermic use of brandy and digitalis, the same remedies with tincture of nux vomica being given internally, and auxiliary measures used.

† Cyanogen Gas has been studied physiologically by B. Bunge. He finds that it kills by paralyzing the centres of respiration, but that it is less powerful in its influence than is hydrocyanic acid, and causes only very feeble convulsions.

Hydrocyanic acid of common medical parlance is the official *Diluted Hydrocyanic Acid*, a colorless, watery solution, containing two per cent. by weight of the anhydrous acid. Its odor and taste are the familiar ones of peach-kernels and bitter almonds; its reaction is faintly acid. As it has a great tendency to undergo spontaneous decomposition, especially under the influence of light, it should be kept in well-stoppered, dark-colored bottles.

*Potassium Cyanide* occurs in white, amorphous, opaque masses, or as a granular powder, odorless when dry, but deliquescing in the air and exhaling the odor of prussic acid. It is readily soluble in water.

#### Official Preparations:

Acidum Hydrocyanicum Dilutum (2 per cent.).....	1 to 3 minims (0.06-0.18 C.c.).
Potassii Cyanidum.....	$\frac{1}{12}$ to $\frac{1}{10}$ grain (5 to 6 Milligm.).
Argenti Cyanidum.....	Not used internally.

*Local Action.*—*Absorption and Elimination.*—Hydrocyanic acid appears to be free from irritant properties, but is a universal depressant poison, capable, when in sufficient amount, of paralyzing all higher tissues, and having, when applied locally, an especially powerful influence upon sensory nerve-endings. It is absorbed with almost instantaneous rapidity through all mucous membranes. Concerning its fate in the body we have no knowledge except that it is either destroyed or eliminated with the greatest rapidity, so that its action is extremely fugacious.

*General Action.*—The symptoms produced by prussic acid in man are so rapid in development and course that usually the patient is dead or convalescent before seen by the physician. The ordinary therapeutic dose produces no distinct manifestations; after the toxic dose the symptoms come on suddenly. In a moment or two the individual falls to the ground insensible and convulsed, the respirations arrested or occurring at long intervals, the eyes salient, the pupil dilated, the mouth covered with bloody froth. If the dose be sufficiently large, death may occur in three or four minutes; if less has been taken, deep insensibility, tetanic or clonic convulsions, dilated pupils, a bloated countenance, cyanosed surface, set jaws, and irregular respiration constitute the chief symptoms. The breathing is mostly convulsive, with deep, forcible expirations, but in some cases it has been stertorous. Death results from asphyxia. After small toxic but not lethal doses of prussic acid, giddiness, lightness of the head, nausea, a quick pulse, and muscular weakness are the chief symptoms.

After a full dose of absolute hydrocyanic acid, the lower animal gasps once or twice, and then instantly falls in a tetanic or clonic convulsion, or else drops motionless and powerless upon its side, heart and lungs ceasing almost at once. After a smaller toxic dose the signs of asphyxia at once manifest themselves, and grow more and more intense, until they end in total arrest of respiration. The heart beats irregularly, often at first slowly and strongly, with intervals of suspension of movement, but always becoming weaker and more rapid in its action, until, after the breathing has ceased, its efforts gradually die away. Ordinarily, three distinct

stages are apparent: a first, very brief one, of difficult respiration, slow cardiac action, and disturbed cerebation; a second, convulsive stage, with dilated pupils, violent convulsions, unconsciousness, loud cries, vomiting, often spasmodic urination and defecation, erections, etc.; and a third period, of asphyxia, collapse, and paralysis, sometimes interrupted by partial or even general spasms.

The slow form of the poisoning follows the exhibition of the poison in an amount just sufficient to kill. After the ingestion of such a dose, no phenomena are offered for some seconds; then the breathing becomes labored and the pulse slow and full. The animal perhaps cries out, and muscular tremblings rapidly grow into clonic and tonic convulsions, which continue at intervals until the third stage—that of collapse—is developed. When the third stage is developed, the anesthesia is marked, affecting first the hind legs, but finally spreading to all parts of the body, and even being complete in the widely dilated pupil. Death finally results from failure of respiration. Recovery may occur even after the conjunctiva has lost its sensibility; the return to life by a subsidence of the symptoms is usually rapid, so that generally in from one-half to three-quarters of an hour the animal will be eating as though nothing had happened. Coullon, however, noted persistence of paralysis, in some cases, for days.

*Blood.*—When prussic acid is added to blood outside of the body it produces a new chemical compound known as cyanohemoglobin. Whether this substance is produced in the body or not is somewhat questionable. During life, however, it has been shown by numerous observers that in early stages of poisoning the blood in both arteries and veins has a bright arterial hue and in the later stages, if death has not occurred too rapidly, a deep venous hue. The last change is due to the failure of respiration. The occurrence of bright red blood in the veins, however, has not as yet been satisfactorily explained.

F. B. Vietz, E. L. Schubarth, J. F. Sobernheim, Coze, and Claude Bernard, have demonstrated the occurrence of the phenomena of red blood in the veins.

According to Gaethgens, the scarlet venous blood of the first stage of the poisoning shows clearly the absorption bands of oxyhemoglobin under the spectroscope, while Preyer has demonstrated that the dark blood of the advanced stages of the poisoning gives only the lines of reduced hemoglobin.

As was first shown by W. Preyer, and subsequently confirmed by Carl Gaethgens, directly after the administration of the poison, in the mammal the venous blood becomes almost immediately of a bright arterial hue, which, however, rapidly darkens until all the blood of the body is venous. If the mammal dies suddenly from cardiac paralysis during the first stage of the poisoning, this excessive arterialization may be found after death, and in cold-blooded animals, the bright color persists for many hours (Preyer). If, however, life is more prolonged, the blood grows dark.

The explanation offered by Hoppe-Seyler that the drug produced a functional paralysis of the red blood-corpuscles seems improbable, in view of the fact of the later occurrence of the reduction of the oxyhemoglobin. Gaethgens has shown, however, that during the stage of red blood there is diminished elimination of carbonic acid from the lungs. There is, however, formed no new chemical compound in the blood, as is shown by the spectroscopic examinations of Preyer, Laschkewitsch, and Hiller and Wagner, and also by the fact, determined by Lecorché and Meuriot, that in the stage of venous blood artificial respiration would restore oxyhemoglobin. It would seem, therefore, that the drug in some way, perhaps by its effect upon the tissues rather than upon the blood, prevents the giving up of oxygen by the red blood-corpuscles. When the dose has been large enough to cause sudden death the bright red hue may persist for some time after death.



As first discovered by Hoppe-Seyler, and afterwards confirmed by Preyer, when hydrocyanic acid is added to blood outside of the body there is produced a new substance giving rise to new spectroscopic lines and without ozonizing power, the so-called *cyanohemoglobin*.

Alterations in the form of the corpuscles of the blood have been suggested as the cause of the changes of the color, Ernst Geinitz having found that, both in the frog and in the mammal, prussic acid distorts the blood-corpuscles. On the other hand, in the observations of Preyer, although such alteration of the blood-corpuscles could be produced in mammalian blood outside of the body, yet in blood drawn immediately after death from prussic acid the corpuscles offered their usual character; a fact confirmed by Hünefeld.\*

Whatever may be the cause of the changes in the blood, the experiments of Lewisson would appear to prove that the action of the poison on the nervous system is a direct one, and not due to these changes in the vital fluid, for the observer mentioned found that prussic acid acted upon the bloodless "salt frog" as upon the normal batrachian.

*Circulation.*—When a moderately large dose of prussic acid is injected into a vein there occurs a marked but fugacious rise of the blood-pressure with slowing of the pulse, followed by a fall of the pressure below the normal and later an extremely rapid pulse. According to Preyer, Laschkewitsch and Lecorché and Meuriot, hydrocyanic acid is a depressant to the heart-muscle and the primary rise of pressure which occurs is, therefore, due probably to a temporary stimulation of the vaso-motor centres. These latter are afterwards paralyzed, as Lazarski has found that galvanization of the sensitive nerve in the late stages of poisoning will not cause a rise of pressure. Lazarski has also found that the slowing of the pulse caused by moderate doses of hydrocyanic acid is prevented by previous section of the vagi and it may therefore be considered that the drug is stimulant to the cardio-inhibitory centres. According to Boehm and Knie, however, the late slowing of the pulse from toxic doses is not affected by vagal section and is probably due to direct action upon the cardiac muscle or its intrinsic ganglia.

*Respiration.*—Hydrocyanic acid acts directly upon the respiratory centres as a depressant, so that in poisoning by it the respiratory movements are lessened from the beginning, and becoming more and more distant finally cease before the heart's action is arrested.

Preyer found that, after division of the vagi, normally lethal doses did not kill, and that when death was brought about by the exhibition of larger doses it was by cardiac arrest. From this he deduces the conclusion that the prime respiratory action of the poison is upon the peripheral ends of the vagi. Preyer's experiments have been partially confirmed by Lecorché and Meuriot; but Boehm and Knie have in a series of experiments found that section of the vagus has no influence upon the respiratory action of the poison, and in this have been confirmed by Jos. Lazarski. Even if investigations had proved the correctness of Preyer's experiments, his conclusion could not be considered established, because we know so

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\* According to E. Ray Lankester (*Pflüger's Archiv*, 1869, 492), when blood is shaken with cyanogen gas, and allowed to stand for two or three hours, the spectrum-changes are exactly the same as after similar treatment of blood with CO. The compound of cyanogen and hematin (Cy,Hb) offers not only the identical spectrum of CO,Hb, but also, like the latter, is unaffected by reducing agents. After the blood stands awhile, according to Lankester, the spectrum of hydrocyanic acid (H,CN) becomes visible in it, and the Cy,Hb undergoes conversion into the cyanohemoglobin (Cy,Hb) of Hoppe-Seyler.

imperfectly the normal relations of the pneumogastrics to respiration. Moreover, Joseph Jones found that while to kill an alligator by the administration of prussic acid required a considerable length of time, its application to the medulla produced within one minute a most powerful expiration, ending in permanent contraction of the muscles of respiration and collapse of the lung. In the experiments of H. Hayashi and K. Muto doses of 15 milligrammes per kilogramme of potassium cyanide caused, in the rabbit, fatal paralysis of respiration at a time when the phrenic and motor nerves were still excitable.

*Nervous System.*—Hydrocyanic acid produces in the frog a condition of complete paralysis in which Kölliker believes that first the brain and next the reflex centres of the spinal cord are affected, although he has demonstrated, as have Funke and Stannius, that the motor nerves and the muscles are both finally paralyzed by the drug. Kölliker has also shown that, when applied locally, the drug paralyzes the peripheral endings of the sensory nerves.

It is a question of interest to decide as to the cause of the convulsions in poisoning by hydrocyanic acid. We have found that they do not occur after section of the cord in parts below the point of section, and that they are therefore cerebral in origin. It is probable that the convulsions are secondary, asphyxial, or due to disturbance of circulation. Laschkewitsch, who opened the thorax of a rabbit so as to expose the heart, maintained artificial respiration, and administered prussic acid; directly after arrest of the heart had commenced the convulsions came on; also in the earlier observation of Coze, the convulsions did not occur until directly after the arrest of the circulation. In frogs poisoned with hydrocyanic acid, convulsions do not take place. Preyer states that after section of the vagi convulsions do not generally happen in mammals, but if artificial respiration be performed they come on.

**SUMMARY.**—When in sufficient concentration hydrocyanic acid is a powerful depressant poison to all the higher tissues. It is absorbed immediately, and acts at once, but its influence is over in a few minutes. In poisoning by it death usually occurs through centric paralysis of the respiration, but the depression of the heart's action is pronounced, and diastolic cardiac arrest sometimes takes place simultaneously with or even before cessation of breathing. It first stimulates, then paralyzes the vagi; it first stimulates, afterwards paralyzes the vaso-motor system. Upon the nerve-centres it has a most pronounced depressing influence, and it is also a paralyzant to the nerve-trunks and to the muscles themselves. There is some reason for suspecting that after the small toxic dose of hydrocyanic acid the paralytic stage is preceded by a very brief stage of excitement, with centric increase of the respiratory activity, rise of the arterial pressure (caused by an influence upon the vaso-motor centres and perhaps upon the heart), and slowing of the pulse from stimulation of the cardiac inhibitory centres. Outside of the body hydrocyanic acid attacks the red blood-corpuscles, forming a new compound, cyanohemoglobin; but the occurrence of this change during life in hydrocyanic-acid poisoning is doubtful.

**Therapeutics.**—Our knowledge of the physiological action of prussic acid does not lead to a belief in its wide applicability to the relief of disease, and we think that clinical experience has demonstrated that it is of little value except in meeting three indications: first, *to allay cough*; second, *to relieve irritation of the gastric nerves*; third, *to allay irritation of the peripheral sensitive nerves*.

Prussic acid has been used very largely to allay cough, either itself or in the form of potassium cyanide. Owing to the extreme fugaciousness of its action, it is, however, of very little real value for this purpose. It is improbable that the effect of a therapeutic dose of the acid lasts over twenty minutes, or of the cyanide over forty-five minutes.

There can be, on the other hand, no doubt as to the value of prussic acid in certain stomachic affections, especially nervous *vomiting* and *gastralgia*. When the pain is accompanied by decided dyspeptic symptoms the remedy will sometimes succeed, but more often fails. Even in the most favorable cases it does not always afford relief; and as the relief when it does occur is immediate, or at least is very soon apparent, it is useless to persist long in the exhibition of the remedy. In these cases its action is probably local, as it certainly is when the acid is employed to relieve itching in *prurigo* and other cutaneous diseases. For this purpose it is used as a wash (one-half to one fluidrachm in one fluidounce); but great care must be taken to avoid constitutional effects, especially when there is any abrasion of the skin. Very serious results are said to have been caused by its absorption when carelessly used in skin diseases.

Prussic acid has been commended as an arterial sedative; but unless given in dangerous doses it has no such action.

**Toxicology.**—The symptoms of prussic-acid poisoning have already been mentioned (p. 276): those of most value from a diagnostic point of view are the sudden occurrence of unconsciousness, the violent convulsions, the general paralysis, the peculiar character of the breathing, expiration being prolonged and forced, and the rapid results. The odor of prussic acid upon the breath is very often, but by no means always, present. When distinct, it is, of course, of great diagnostic value. Leaving out of sight the cyanides, the only poison with which prussic acid could well be clinically confounded is nitrobenzol. The distinction is often very difficult, large doses of the latter substance killing almost as quickly as prussic acid and inducing analogous symptoms. Caspar advises that after death the body be left open, exposed to the air, as the odor of prussic acid disappears rapidly, while that of nitrobenzol is persistent. The diseases with which the poisoning may be confounded most readily are some forms of *apoplexie foudroyante*, and sudden failure of the heart's action. The diagnosis may, during life, be almost impossible. It has been asserted that stertorous breathing does not occur in prussic acid poisoning; but it has been present in several reported cases.\*

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\* See *Taylor's Medical Jurisprudence*, Philadelphia, 1873, 363.



An autopsy, however, ought generally to enable the physician to determine whether the case has or has not been one of prussic acid poisoning, if the symptoms during life are known.

A curious case of temporary *hemipia*\* apparently caused by the fumes of hydrocyanic acid, is reported.

The period at which death may occur after the ingestion of the poison is set down by Lonsdale at from one to fifty-five minutes; but a case has been observed by Hilton Fagge, in which the fatal result was put off for at least an hour and a quarter after the ingestion of hydrocyanic acid. After death the body often presents a livid surface, bloated countenance, fixed glassy eyes with dilated pupils, and clinched fingers; sometimes it offers nothing worthy of note except excessive rigidity, and the face may be very pale. When opened, the odor of prussic acid is generally, but not always, emitted; the mucous membrane of the stomach is very commonly found much congested, and the dark or cherry-colored liquid blood usually everywhere fills up the veins. The heart is soft and flaccid.

The treatment of poisoning by prussic acid is of little avail. Of the several chemical antidotes which have been proposed, hydrogen dioxide is the most practicable.† But such is the rapidity of absorption that the case is usually terminated before the antidote can be obtained. The asserted physiological antagonism of atropine has been disproved by Keen and by Boehm and Knie. The stomach should, if possible, be emptied or washed out with a thirty per cent. hydrogen-dioxide solution if at hand, and the hypodermic use of atropine and strychnine as respiratory stimulants might be tried; the inhalation of the vapors of ammonia, and the free exhibition of ammonia by the mouth and by injection into the veins, may be practised. Artificial respiration has been found very successful by Preyer, and by Boehm and Knie, in animals, and should always be assiduously practised. Next to it in importance is the use of the alternate cold and hot douche, about a half of a small bucketful of cold water and the same quantity of very hot (115° F.) water being dashed upon the chest in rapid succession. There is considerable experimental evidence to show that the sodium hyposulphite is capable of following prussic acid, cyanides, nitrobenzol, and other nitrites into the system and there decomposing them, but we know of no case in which the antidote has been used upon man. As it is harmless it might be given hypodermically.‡

When potassium cyanide is taken into the stomach, the acids there present convert it into prussic acid, and the same change probably occurs, although more slowly, even when the salt is injected directly into the blood-vessels. The physiological, therapeutical, and toxicological properties of this salt are similar to those of prussic acid.§

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\* See *B. M. J.*, 1884, i, 409.

† See E. Merck, *Merck's Arch.*, 1900, ii, 94.

‡ See S. Lang, *A. E. P. P.*, 1895, Bd. xxxvi.; J. F. Heymans and P. Masoin, *A. I. P.*, 1897, iii, fasc. 1 and 2; R. Verbrugge, *A. I. P.*, v, fasc. 3 and 4; and J. Meurice, *A. I. P.*, vii, fasc. 1 and 2.

§ Poisoning has occurred from the inhalation of the vapors of the cyanide and from absorption through the hands (*Brit. and For. Med. Chir. Rev.*, July, 1876, 231).

Death, however, does not occur so soon as from hydrocyanic acid, and insensibility is sometimes not manifested for several minutes. Five grains of the salt have caused death but fifty grains have been recovered from. (See McKelway.)

**BITTER ALMONDS** (*Amygdala Amara*) yield a volatile oil, *Oleum Amygdalæ Amaræ*, Oil of Bitter Almonds; of a yellowish color, bitter, acrid taste, with a strong odor of prussic acid. This volatile oil consists of not less than 85 per cent. benzoic aldehyde contaminated with various substances, of which the most important, prussic acid, is present in the proportion of from two to four per cent. Two drachms of the commercial oil are said to have caused death in ten minutes. Very properly, under the name of *Benzaldehydum*, U. S., *Benzaldehyde*, the pure benzoic aldehyde, produced synthetically or obtained from natural oils, has been recognized in the last edition of the U. S. Pharmacopœia. This is a colorless, strongly refractive liquid, having a bitter odor and a burning taste. The official oil and benzaldehyde are very seldom used except as flavoring agents.

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### ORDER III.—NUTRIANTS.

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#### FAMILY I.—ASTRINGENTS.

ASTRINGENTS are those drugs which cause contraction of living tissues. That they do not act, as has been supposed, either by coagulating albumin or by calling into action the muscular function is demonstrated by the transitoriness of their effects, and by the fact that they influence tissues containing no muscular fibre. Every living soft tissue appears to possess a normal degree of condensation, which may be departed from on either hand: when this happens, in the one case the part is said to be relaxed, in the other to have its tonicity increased, or to be astringed. The action of astringents is always a *local one*,—*i.e.*, produced not through the intervention of the nervous system, but by direct contact with the part affected. A pure astringent should be capable of doing nothing beyond inducing contraction; but in reality there is scarcely such a drug. Astringents are, when applied too freely, irritants.

The concordant experimental results reached by M. Rosenstein and by R. Heinz show that medium solutions of tannic acid, alum, and the salts of lead, zinc, iron, copper, and mercury contract the blood-vessels by a direct action. When, however, the solutions are too strong, according to Heinz, this contraction is followed by dilatation. Both experimenters state that the silver nitrate is the most powerful in its influence, producing an almost permanent contraction. According to Rosenstein, acids cause dilatation of the capillaries.

The clinical results obtained by the use of astringents in the treatment of inflammation can hardly be due to their action upon the blood-vessels, but seem to find more appropriate explanation in the discovery of Heinz, that, locally applied, they decidedly check the out-wandering of the white blood-corpuscles, probably, as he thinks, by modifying the wall of the blood-vessel.

The chief indication for the use of an astringent is the *existence of relaxation*. Local relaxation is commonly due to previous over-excitement. Thus, a throat is relaxed after over-use, or after inflammation.

Astringents are more efficient as local than as general remedies, but in cases of inflammation care must be taken to use them in such a way that they shall not act as irritants. Applied too soon or too vigorously, they may do harm. These remarks are scarcely applicable to some of the mineral astringents, such as lead acetate or silver nitrate, which really appear to have sedative properties, and may with care be used advantageously in all stages of inflammation, when-



ever there are distention and relaxation of the blood-vessels, although the general action of the part be that of nutritive excitement.

Closely allied to relaxation is over-secretion, and astringents are constantly used to *check morbid discharges*. Indeed, these discharges are often simply the result of relaxation. Thus, Asp has experimentally proved that division of the intestinal nerves and consequent paralysis and relaxation of the vessels are followed by free watery secretion. In such cases the indication for astringents is very plain. But when a morbid discharge represents a high degree of inflammation, the same care must be practised in the use of astringents as in treating other local inflammations. Especially is this true since free secretion is often nature's method of relieving local inflammation. Thus, when abnormal alvine discharges are dependent upon intestinal relaxation, astringents are most valuable, but when they are dependent upon enteritis or colitis, astringents may do harm.

If the morbid discharge by its profuseness endangers life, as in *serous diarrhæa*, astringents are urgently demanded. Very rarely, if ever, are these discharges other than paralytic in their origin; even, however, if they be due to over-action, an astringent may be necessary to check their excessiveness.

Another indication for the use of astringents is to *check hemorrhage*, and the same general reasoning is applicable to this as to the other indications. Hemorrhage dependent upon over-action demands other treatment than by astringents. Sometimes in these cases it is necessary, however, to check the hemorrhage at all hazards, and then astringents may be used in conjunction with other measures, although they may be to some extent contraindicated. Some of the astringents are employed locally to check hemorrhage due to traumatic or other ruptures of vessels. In such cases the astringents are employed as *styptics*, and do not act so much by their astringency as by coagulating the albumin of the blood and thus forming a clot and mechanically arresting the flow.

Under certain circumstances there seems to be a general relaxation or loss of tone throughout the whole system, which may be best met by a consentaneous use of tonics and astringents.

### VEGETABLE ASTRINGENTS.

The active principle of the vegetable astringents is tannic acid, and as it is almost their sole therapeutic principle and represents them very closely, it seems proper first to consider it, and afterwards to point out any especial therapeutic virtues the crude drugs of the class may possess.

#### TANNIC ACID.

There are two generic varieties of tannic acid, the *gallo-* and the *kino-tannic*: of these the former yields, upon exposure to the air in a moist state, *gallic acid*, the latter a *gelatinous, inert* substance. They

are further distinguished by the color of the precipitates which they yield with the persalts of iron; gallo-tannic acid producing a blue-black, kino-tannic a green-black color.

The official tannic acid—the gallo-tannic acid—is obtained by treating powdered galls with washed ether, which on standing separates into two strata, the upper of which is ethereal and contains chiefly the coloring-matter and other impurities. The lower watery stratum contains the tannic acid, which is recovered by evaporation.

Commercial tannic acid is a light, feathery, *non-crystalline* powder, of a yellowish-white color, a faint odor, and an astringent, somewhat bitter taste. When absolutely pure, it is colorless and free from odor or taste other than that of astringency. Its reaction is strongly acid, and it unites freely with both organic and inorganic bases. It is very freely soluble in water, glycerin, and alcohol. With salts of the alkalis it produces a whitish precipitate (tannates), very soluble in acetic acid; with persalts of iron, a black (bluish or greenish) precipitate.

#### Official Preparations:

Acidum Tannicum.....	10 to 20 grains (0.6–1.2 Gm.).
Trochisci Acidi Tannici.....	Each 1 grain (0.06 Gm.).
Glyceritum Acidi Tannici (20 per cent.)....	Local use.
Unguentum Acidi Tannici (20 per cent.)....	Local use.
Collodium Stypticum (20 per cent.).....	Local use.

**Physiological Action.**—Applied locally, tannic acid is a very powerful astringent, causing contraction, and in the case of a mucous membrane, great dryness. Sometimes, when it is used very freely, its irritant influence seems to overcome its astringent action, and we have seen diarrhoea result from its administration. Several experimenters (Rosenstein, Fikentscher) have denied that it causes contraction of the blood-vessels, because when they applied it to the exposed mesentery of a “Cohnheim frog,” stasis of the blood, with dilatation of the vessels, not preceded by contraction, occurred. Daniels, however, using rabbits, obtained different results, and Lewin has shown that the method of experimentation was faulty. Clinical experience proves that tannic acid applied to relaxed mucous membranes affects their whole substance.

**Absorption and Elimination.**—Although it was formerly believed that owing to the activity with which tannic acid coagulates albumin it was incapable of absorption, under certain circumstances a small amount of an alkaline tannate may be absorbed and circulate in the blood; but although a small portion of it may get into the blood as a tannate, what is absorbed is chiefly various decomposition products. Gallic acid has been found in the urine after the administration of tannic acid, but according to Morner the amount is less than one per cent. of the tannic acid ingested. When given in large amounts it mostly escapes absorption, and passes out with the feces unchanged.

Thrown rapidly into the blood, tannic acid causes a fatal thrombosis; but Lewin asserts that when it is injected slowly and in moderate quantities the resulting

albumin tannate is held in solution by the alkaline carbonates. He has also discovered that while tannin, in five-per-cent. solution, precipitates peptones out of watery solution, it is powerless in the presence of hydrochloric acid. Assuming the correctness of the investigations of Lewin, it is plain that tannic acid, when put in the stomach in small doses, must to some extent be absorbed unchanged. Lewin also asserts that it is, at least in part, eliminated unaltered, as he has frequently recovered it from the urine. At the same time it seems very probable that most of the tannic acid is converted into gallic acid, either in the stomach before absorption or subsequently in the system, since in the viscera of a rabbit poisoned with it, Schroff found only gallic acid; according to Clarus, the greater part of ingested tannic acid can be recovered from the stools as albumin tannate or as gallic acid. The recent researches of Stockman afford a possible reconciliation of the results of Lewin with those of the older observers. Stockman finds that when tannic acid is given to the lower animals only a trace of it appears in the blood, while gallic acid can be obtained in abundance from the urine, with occasionally a small amount of tannic acid. If, however, sodium tannate be given, tannic acid appears in abundance in the urine, with a little gallic acid. The explanation offered by Stockman of this is probably correct,—namely, that tannic acid is usually converted in the stomach into an albuminous tannate, which is dissolved with great difficulty in the intestinal juices, so that time is afforded for the conversion of the tannic into gallic acid, whereas an alkaline tannate is absorbed at once and rapidly eliminated unchanged.

Wöhler and Frerichs have also found gallic acid with pyrogallic acid in the urine after the exhibition of tannic acid.

After its conversion and absorption tannic acid still possesses astringent properties. Lewin has shown that in frogs poisoned with it the muscles are shortened and narrowed, and when loaded stretch less and recover their original length more nearly than do normal muscles. Küchenmeister and Hennig state that in poisoned cats the spleen is notably diminished in size and increased in firmness; and Lewin has found in rabbits that tannic acid causes primary arrest of the urinary secretion, followed by a marked increase of the flow.

**Therapeutics.**—As tannic acid undergoes in the system partial conversion into gallic acid, the latter is to be preferred to it when the part to be acted on can be reached only through the circulation. As a local application, tannic acid is much more powerful than gallic acid. Locally applied it may be used to overcome relaxation, as in *spongy gums*, *mercurial sore mouth*, *hemorrhoids*, and *chronic sore throat*. To check hemorrhage it may be used whenever the source of the flow can be reached directly, as in *epistaxis*, *hematemesis*, *hemorrhage from the bowels*, etc. To arrest excessive secretion it may be employed locally in *leucorrhæa*, *diarrhæa*, *old abscesses*, *chronic ulcers*, *excessive perspiration*, *osmidrosis*, and various diseases of the skin. It is also often very useful for the purpose of hardening parts exposed to friction, as in cases of *sore nipples* and *tender feet*.

As an *antidote* it is useful in poisoning by various metals, especially antimony and iron. It is also a chemical antidote for the poisonous alkaloids; but, as the compounds it makes with them are slowly dissolved by the fluids of the alimentary canal, it must always be followed by emetics and cathartics.



**Administration.**—When given to act on the stomach, as in hæmatemesis, tannic acid should be in powder. When the bowel is to be influenced, as in diarrhœa, the preparations of the various plants mentioned below are preferable as the colloid matter of the cruder galenicals protects the tannin from immediate precipitation in the stomach.

**Toxicology.**—Tannic acid can scarcely be called poisonous; although Rollet reports the case of a young girl in whom a very large quantity of it induced severe gastric and abdominal pains, with obstinate vomiting and constipation, fever, and general malaise. Both Schroff and Judell assert that eighty grains of it cause no symptoms of importance in the rabbit.

### GALLIC ACID.

Gallic acid is a white, powdery substance, in fine acicular prisms, soluble in 83 to 86 parts of water, in three parts of boiling water, and freely soluble in alcohol and in ether. Its taste is acidulous and astringent.

According to the usual method, gallic acid is prepared by the exposure of moistened powdered nutgalls in a warm place for a month. A species of fermentation, with the development of a peculiar fungus, is said to occur, during which oxygen is absorbed, carbonic acid is evolved, and glucose and gallic acid are produced. M. Sacc has, however, denied this, affirming that the change is simply one of hydration, tannic acid being an anhydride of gallic acid. Tannic acid also may rapidly be converted into gallic acid by the action of dilute sulphuric acid.

Gallic acid produces with persalts of iron a bluish precipitate, with lime-water a whitish precipitate, changing to blue and then to violet or purplish,—all of these precipitates being gallates. It does *not* coagulate gelatin or albumin, and is, therefore, not a styptic. As an astringent it is less powerful than tannic acid. It escapes from the body through the kidneys.

Acidum Gallicum.....15 to 30 grains (1-2 Gm.).

**Therapeutic Action.**—Gallic acid is not nearly so efficient as tannic acid, when applied locally, but should always be preferred when the part is to be reached through the medium of the circulation. It is useful as an astringent in *hemoptysis*, *hematuria*, *colliquative sweats*, etc. It has been recommended in *bronchorrhœa* and in the profuse expectoration of *chronic phthisis*. In our hands, however, it has completely failed in the latter affections. In *Bright's disease*, when there is an abnormally large secretion of highly albuminous urine, it may lessen very materially the excretion of albumin.

The following drugs which are recognized by the U. S. Pharmacopœa depend for their activity chiefly upon some form of tannic acid.

**Galls** are produced on several varieties of oak trees by the wounds of various insects. The official nutgall is developed on the *Quercus infectoria* by the punc-

tures of the *Cynips Tinctoria*. There are two varieties of galls, derived chiefly from the Levant: the blue or green, which are the young galls gathered before the ova of the fly are hatched, and the white galls, which are light hollow bodies from which the young cynips has escaped. The latter contain but little tannic acid and the U. S. Pharmacopœia, therefore, only recognizes the green variety. These are of a bluish olive green color, from the size of a pea to that of a hickory nut, externally smooth or more commonly marked with tubercles. They contain from fifty to eighty per cent. of gallotannic acid.

*Tinctura Gallæ* (20 per cent.).....1 fluidrachm (4 C.c.).  
*Unguentum Gallæ* (20 per cent.).....External use.

**Gambir**, also sometimes known as Pale Catechu, is an extract derived from *Ourouparia Gambir*. The extract occurs as irregular masses or cubes of a reddish or grayish-brown color with a bitter and very astringent and afterwards a sweetish taste. It contains from twenty-five to fifty per cent. of kinotannic acid.

*Tinctura Gambir Composita* (5 per cent.)..2 fluidrachms (8 C.c.).  
*Trochisci Gambir*.....Each contains 1 grain (0.06 Gm.).

**Kino** is the dried juice of *Pterocarpus Marsupium*, an East Indian tree. It occurs in small irregular shining reddish fragments with a highly astringent taste, at first bitterish, but afterwards sweetish. It contains from sixty to seventy-five per cent. of kinotannic acid.

*Tinctura Kino* (5 per cent.).....1 to 4 fluidrachms (4-15 C.c.).

**Hematoxylon** is the heart wood of the *Hematoxylon campechianum*, or log-wood tree, a native of Central America. It is dense heavy wood of a deep reddish-brown color, containing besides kinotannic acid a crystalline principle hematoxylin, which, when pure, is yellow but readily yields red or purple dyes.

According to Combemale, hematoxylin is capable of causing a fatal intoxication, commencing with rigors and fever and ending in vomiting, anuria, coma and collapse. Its taste is sweetish, somewhat like that of licorice, and astringent.

*Extractum Hæmatoxyli*.....15 to 30 grains (1-2 Gm.).

The following formula offers an efficient and elegant remedy for *diarrhæas* of relaxation; the proportions may be varied to suit individual cases. *R* Ext. hæmatoxyli,  $\mathfrak{z}$ ii; Acid. sulph. aromat.,  $\mathfrak{f}\mathfrak{z}$ iii; *Tinct. opii camph.*,  $\mathfrak{f}\mathfrak{z}$ iss; *Syrupi zingiberis*, q. s. ad  $\mathfrak{f}\mathfrak{z}$ vi. *M.*—Dose, a tablespoonful, properly diluted.

**Rhus Glabra**.—The U. S. Pharmacopœia recognizes the berries of the sumac or *Rhus glabra*. They contain from six to twenty-five per cent. of tannin and are especially useful as a basis of mouth-washes or gargles on account of their pleasant taste.

*Fluidextractum Rhois Glabræ*.....15 minims (1 C.c.).  
 Locally it may be used in strengths of 15 to 30 per cent.

**Krameria**, or rhatany, is the dried root of the *Krameria triandra*, *Krameria ixina* or *Krameria argentea*, South American shrubs. It contains from five to fifteen per cent. of a peculiar tannic acid.

*Extractum Krameriaë*.....5 to 10 grains (0.3-0.6 Gm.).  
*Fluidextractum Krameriaë*.....10 to 20 minims (0.6-1.2 C.c.).  
*Syrupus Krameriaë* (45 per cent.).....20 to 30 minims (1.2-2 C.c.).  
*Tinctura Krameriaë* (20 per cent.)..... $\frac{1}{2}$  to 1 fluidrachm (2-4 C.c.).  
*Trochisci Krameriaë*.....Each 1 grain (0.06 Gm.).

**Oak.**—The bark of many species of oak trees contains notable proportions of tannic acid. The U. S. Pharmacopœia recognizes only the bark of the *Quercus alba* or white oak. This contains from five to ten per cent. of quercitannic acid. It is used chiefly as a means of making cheap astringent infusions for external application.

Fluidextractum *Quercus*.....15 minims (1 C.c.).  
Locally a 25 to 50 per cent. solution may be employed.

**Hamamelis**, or witch-hazel, is an abundant native bush from which various preparations are made which enjoy extraordinary popularity for local applications. Their virtue depends chiefly upon the faith with which they are applied. The Pharmacopœia recognizes both the bark and the leaves of the *Hamamelis virginica*.

Aqua *Hamamelidis*.....External use.  
Fluidextractum *Hamamelidis Foliorum*..... $\frac{1}{2}$  to 2 fluidrachms (2-8 C.c.).

**Geranium** is the rhizome of the *Geranium maculatum* or cranesbill. It contains from ten to twenty-five per cent. of gallotannic acid.

Fluidextractum *Geranii*..... $\frac{1}{2}$  to 1 fluidrachm (2-4 C.c.).

**Rose Leaves.**—The dried petals of the *Rosa gallica*, or red rose, also contain a small percentage of tannin, but are used chiefly for their pleasant flavor.

Fluidextractum *Rosæ*..... $\frac{1}{2}$  to 2 fluidrachms (2-8 C.c.).  
Confectio *Rosæ*.....Excipient for pills.  
Mel *Rosæ*.....Vehicle.  
Syrupus *Rosæ*.....Vehicle.

A number of unofficial compounds of tannic acid have come into vogue, some of them of great practical value.

**Tannalbin.** *Tannin albuminate*.—This is a light-brown powder, insoluble in water or the gastric juice, but decomposed by the alkaline juices of the intestines with the liberation of its constituents. It is tasteless, odorless, and non-irritant. It is a very valuable remedy in the treatment of *intestinal catarrh* and *relaxation* requiring the use of an astringent, acting immediately, persistently, and effectively, and affording in many cases an excellent combination with bismuth subnitrate. It has been recommended also in renal conditions associated with an excessive discharge of albumin. Dose, twenty to forty grains, in powder (1.2-2.5 Gm.).

**Tannacol.** *Gelatin tannate*.—A tasteless, odorless powder, probably identical in its therapeutic application to tannalbin, although Rosenheim affirms that it is superior in that it is less apt to be affected by the gastric juice, and is of greater uniformity of constitution. Dose, fifteen to thirty grains (1-2 Gm.).

**Tannopine.** *Tannon*.—A combination of tannic acid and urotropin, which is said to contain eighty-seven per cent. of the acid, and, passing unchanged through the stomach, to undergo decomposition by the alkaline juice of the alimentary canal. It has been strongly recommended by Schreiber and other clinicians in the treatment of all forms of *diarrhœas* requiring an intestinal astringent. Dose, ten to fifteen grains (0.6-1 Gm.).

**Tannoform.**—The *tannoforms* are combinations between tannins and formaldehyde. Commercial tannoform is the condensation product of gallotannic acid and formaldehyde. It is a light, pinkish-white powder, which is believed to be decomposed by the alkaline juices of the intestines with the setting free of tannic acid and formaldehyde, and to act, therefore, as an astringent and antiseptic. It



has been very highly recommended by numerous practitioners in *tuberculous* and other *diarrhas* requiring an astringent, both in adults and in children, given in doses of one-half to one grain (0.03–0.06 Gm.), in capsules, three times a day.

There is also much testimony as to the value of tannoform as an external remedy. According to K. Ullmann, confirmed by F. Merz, tannoform is extremely efficient in *hyperidrosis* of the feet; a foot-bath should be used just at bedtime and a powder, composed of one part of tannoform and two parts of talc, should be well rubbed in between the toes and over the feet, daily for eight days. The effect is said to last many weeks. Tannoform has also been used as a local remedy in various external *ulcerations*, also *eczemas*, and other affections of the skin.

### ACETIC ACID.

Absolute acetic acid, or as it is commonly called, glacial acetic acid, is at temperatures above 60° F. a clear colorless liquid with a strong pungent odor like that of vinegar and an intensely acid, caustic taste. At 59° F. it becomes a crystalline solid. It has a specific gravity of 1.049. The diluter solutions of acetic acid are liquids at all ordinary temperatures. Vinegar contains from five to ten per cent. of acetic acid and therefore corresponds approximately in strength with the official dilute acetic acid.

#### Official Preparations:

Acidum Aceticum Glaciale.....Not used internally.

Acidum Aceticum (36 per cent.).....Not used internally.

Acidum Aceticum Dilutum (6 per cent.)..... $\frac{1}{2}$  to 1 fluidrachm (2–4 C.c.).

*Local Action.*—The strong solutions of acetic acid are intensely irritant, and the glacial acetic acid actively escharotic,—in a measure, no doubt, owing to its properties of dissolving gelatin and gelatinous tissue and of effecting a partial solution of albuminous matters.

Dilute acetic acid or its equivalent, vinegar, acts upon the skin as a powerful stimulant and astringent, causing contraction of the vessels and great whiteness, so that it is often very useful as a topical application in various forms of *dermatitis*, especially *sunburn*, and also in *bruises* and *sprains*. We have found it, diluted with from one to four parts of water, a very grateful drink in *hematemesis*, and very effective in arresting the flow of blood. Diluted with two or three times its bulk of water, it is occasionally employed as an injection against *seat-worms*; but the infusion of quassia is preferable.

The use of acetic acid as a caustic will be spoken of under the heading of Escharotics.

**Toxicology.**—Acetic acid in any of its more concentrated forms is a corrosive poison, and death has been produced by it in at least one case (Orfila). The symptoms resemble those caused by mineral acids, and the treatment is exactly similar,—neutralization by an alkali or its carbonate, or by some substance, such as soap, containing an alkali, and the meeting of indications as they arise.

**AGARIC.**—Under the name of Agaric various species of fungi belonging to the genus *Boletus* have been employed from time to time in medicine. Of these the *white agaric*, or *purging agaric* of writers, is obtained from *Boletus laricis*, the fungus

of the European larch. It contains a whitish, very bitter acid, variously known as *agaric acid*, or *agaricinic acid*, slightly soluble in cold water, moderately so in hot water. According to the researches of Hofmeister, agaric acid has upon the lower animals little influence except in arresting the secretion of sweat by paralyzing the peripheral nerves of the sweat-glands. Both the impure extract, known in commerce as *agaricin*, and agaric acid have been extensively used for the purpose of arresting *colliquative sweats*, and in our experience have proven valuable remedies. The only untoward effect ever produced, even by the largest dose, is irritation of the gastro-intestinal canal. Two to five grains (0.13–0.3 Gm.) of the agaricin may be given three times a day, commencing with the smaller dose and increasing. According to Hofmeister, the dose of the pure acid is from one-fifteenth to one-third of a grain (0.004–0.02 Gm.).

**COTARNINE HYDROCHLORATE.** *Stypticin*.—This salt, which is obtained by oxidizing narcotine, occurs in yellow crystals, readily soluble in water and alcohol. Falk found that cotarnine caused in frogs paralysis by depression of the motor side of the spinal cord, and in warm-blooded animals acts as a depressant both upon the cerebral cortex and motor cord, causing narcosis with paralysis. He further determined that it has no direct influence upon the circulation; and that upon the respiration it acts as a primary stimulant and secondary depressant, causing death by central asphyxia when given in toxic dose. Abundant clinical evidence has been published to show that cotarnine is a valuable remedy, as first stated by Freund, in *menorrhagia* as well as in *pulmonic* and other internal *hemorrhages*. It is said, also, to be a powerful local hemostatic. *Cotarnine gauze*, or absorbent cotton saturated with cotarnine, has been greatly praised by dentists and surgeons.

As Mohr in his experiments with the drug failed to produce uterine contractions it seems probable that cotarnine arrests hemorrhage by some sort of astringent action, or by directly affecting the blood; but further physiological investigation is imperative for decision. In *excessive menstruation* half a grain may be given three or four times a day for four days before the expected discharge; the dose being increased to one grain when menstruation appears. In *hemoptysis* three grains may be administered at once subcutaneously, and repeated in half an hour if required.

## MINERAL ASTRINGENTS.

### ALUMINUM.

The salts of aluminum are all possessed of more or less active astringent properties. The one most frequently used and also one of the most powerful is the double sulphate of aluminum and potassium or *alum*.

Owing to the cheapness of ammonia the double salt of alumina and ammonium has been largely substituted for the true alum, which contains potash and is alone recognized by the U. S. Pharmacopœia. The physical qualities of the two salts are identical, but the ammonia alum, when triturated with lime, betrays its nature by the evolved gas. Alum occurs in octahedral colorless crystals, which are often aggregated into large masses. Its taste is astringent, acidulous, and sweetish. It is soluble in nine parts of water at 59° F. and in one-third part of boiling water. It is slightly efflorescent, and when heated parts with its water of crystallization and is converted into a white powder (Dried Alum). The alkalies and their carbonates, lime, magnesia, and its carbonate, potassium tartrate, and lead acetate are *incompatible* with alum.

*Aluminum sulphate* usually occurs in flattened crystalline cakes, of a sour-sweetish, somewhat astringent taste and acid reaction. It is soluble in twice its weight in water. It is an irritant active astringent, with some germicidal power. Its solution, in strength varying from half an ounce to the pint up to saturation, has been used as a local application for *foul ulcers*, *leucorrhœa*, and other allied diseases. In solid form, or even in saturated solution, it is very feebly caustic.

*Aluminum hydroxide* is a white, amorphous, odorless, tasteless, permanent powder, insoluble in water and alcohol, which has been used as a feebly astringent, desiccant powder in inflammatory skin conditions.

#### Official Preparations:

Alumini Hydroxidum.....	External use.
Alumini Sulphas.....	External use.
Alumen (Alum).....	10 to 20 grains (0.6-1.2 Gm.).
Alumen Exsiccatum (Dried Alum).....	External use.

**Physiological Action.**—According to the statements of G. B. Wood and A. Stillé, aluminum can be detected in the urine of persons to whom alum has been given, so that it or its derivatives must find a way into the blood. In dilute solution it is a powerful astringent; in concentrated form, irritant; as dried alum, mildly corrosive. In large dose in the lower animals it produces violent gastro-intestinal irritation, and is capable in man of causing death, preceded by violent vomiting, bloody purging, and hematuria (Kramolik). One ounce and five drachms of burnt alum caused death in eight hours.

**Therapeutics.**—Internally alum is of no value in practical medicine, except it be in *colica pictorum*, in which it is asserted by authority that it is a valuable remedy even though there be no lead in the *primæ viæ* to be precipitated by it as a sulphate. As a local drug it is of especial value as a styptic by virtue of its powerful coagulative influence on albumin; and we have known it usefully given by atomization in *hemoptysis*. It is sometimes used in various *anginas* and other inflamed conditions of the mucous membrane, but is so irritant and attacks so strongly the teeth as to greatly lessen its value.

In *colliquative sweats*, sponging at bedtime with alum-water, or, still better, the taking of an alum-water bath, will often materially aid in restoring the lost tone to the skin. In *chronic ulcers* with exuberant spongy granulations, and in certain conditions of *conjunctivitis*, alum curd is often applied with benefit. When it is desired to exert an astringent action upon the internal organs, alum is not useful. As a mechanical emetic it is too uncertain to be of much value. *Alum curd* may be made by dissolving two drachms in a pint of milk and straining, or by rubbing the alum with white of egg. *Dried alum* is sometimes used as a very mild escharotic for the destruction of exuberant granulations in ulcers.

Aluminum hydroxide is much less irritant than alum and also less actively astringent. It is useful in the form of an ointment in minor *burns* and various irritations of the skin.



# LEAD.

There are five salts of lead, exclusive of the plasters, which are recognized by the Pharmacopœia.

*Lead acetate* or *Sugar of lead* occurs in transparent, acicular, often aggregated, crystals, of a sweet, styptic taste. It is soluble in water, to which it usually imparts a slight milkiness. From its solution it is precipitated black by sulphuretted hydrogen, white by soluble carbonates, chlorides, and sulphates, and bright yellow by potassium iodide. It is also incompatible with the mucilage of slippery elm, but scarcely so with that of flaxseed or of pith of sassafras.

The solution of lead subacetate, sometimes known as Goulard's Extract, is made by boiling lead acetate and lead oxide together. It contains twenty-five per cent. of lead subacetate. The approximate formula is  $Pb_2O(CH_3COO)_2$ . The liquor plumbi subacetatis dilutum contains but one per cent. of lead subacetate and is too feeble for any use. Neither of these preparations is used except externally.

*Lead nitrate* occurs in white, nearly opaque, octahedral, very heavy crystals, soluble in two parts of water at 59° F., and in 0.75 part of boiling water; almost insoluble in alcohol. Used chiefly as a disinfectant.

*Lead oxide* or *Litharge*, which is prepared by blowing air through melted lead, occurs in small yellowish or orange-colored scales, which are insoluble in water and alcohol, but are soluble in acetic or dilute nitric acid and in a warm solution of the fixed alkalies. It is occasionally used as a desiccant astringent powder for ulcers, but its chief employment in medicine is in the making of *Lead Plaster*, which consists chiefly of lead oleomargarate. Lead plaster occurs in grayish, cylindrical rolls, which become adhesive at the temperature of the body, and, spread upon kid, is sometimes used as a protective to parts exposed to pressure, or to superficial ulcers or abrasions.

*Soap Plaster* is made by the addition of soap to lead plaster. It is employed chiefly as a protective.

*Lead carbonate* is a heavy, white, tasteless powder, insoluble in distilled water but slightly soluble in water containing carbonic acid. Rubbed up with linseed oil it constitutes white lead paint. An ointment containing ten per cent. was formerly official.

*Lead iodide* is a heavy yellow powder, insoluble in water, without odor and taste. It has probably no therapeutic virtues, though occasionally used as a local application to ulcers.

## Official Preparations:

Plumbi Acetas.....	1 to 3 grains (0.06-0.2 Gm.).
Plumbi Iodidum.....	Not used internally.
Plumbi Oxidum.....	Not used internally.
Liquor Plumbi Subacetatis [Lead Water; Goulard's Extract].....	External use.
Liquor Plumbi Subacetatis Dilutum.....	External use.
Emplastrum Plumbi.....	External use.
Emplastrum Saponis.....	External use.
Ceratum Plumbi Subacetatis.....	External use.

When a soluble salt of lead is applied to a part in not too concentrated solution, it acts as an astringent and sedative. Owing to the contraction of the vessels which is induced, the tissue becomes blanched and any inflammatory action which may be present is remarkably affected. When in concentrated solution, the mildest preparations of lead are capable of acting as irritants, increasing or even originating inflammation. When the salts of lead are taken internally in therapeutic doses, no decided symptoms are generally induced, except a diminution of the secretions, especially of those of the alimentary canal. Sometimes, when full therapeutic doses are exhibited, a slight lowering of the frequency and force of the pulse is said to result, but we have never witnessed this. The insoluble are much less irritant than the soluble lead preparations.

**Therapeutics.**—The salts of lead are used for their astringent action and also as mechanical protectives. The insoluble salts are much less actively astringent than the soluble salts. Of the latter, for internal administration, preference is given to the acetate; although commended by G. B. Wood in the treatment of *hemoptysis*, practically the only condition in which it is at present employed is in the treatment of *diarrhæa*. On account of its sedative properties, when the purging is attended by inflammation it is one of the most serviceable of all the astringents, and owing to the promptness of its action it is also very valuable in cases with profuse serous discharges. It is given in pill form, frequently combined with opium.

The solution of lead subacetate, commonly known as "lead water," is a very popular external application in cases of *sprains* and *bruises* as well as in superficial *inflammation*. For this purpose it should be diluted with from four to ten times its bulk of water or alcohol. The official diluted solution is too weak to be of value.

Lead nitrate forms the base of Ledoyen's disinfectant solution. It acts by decomposing the sulphuretted hydrogen, itself being converted into a lead sulphide. Lead nitrate is frequently used in the treatment of *onychia maligna*; the dead part of the nail should be cut away and the powdered nitrate thickly sprinkled over the surface; after a few days the slough separates, leaving a skin surface upon which the new nail soon forms. Sometimes more than one application is required.

The insoluble lead carbonate is used to some extent as a sedative protective application, especially in the treatment of *burns*. For this purpose an ointment may be employed. Care must be taken in its use, however, when a large surface is involved, as lead colic has been caused by its absorption.

Lead plaster is sometimes used as a protective to parts exposed to pressure. It also enters into the composition of adhesive and soap plasters, which are used chiefly for mechanical purposes.

**Toxicology.**—Acute lead-poisoning is usually produced by a soluble salt, notably the acetate,\* but a case reported by Freyer

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\* According to Husemann (*Handbuch der Toxicologie*), the *poudre de succession*, so famous during the reign of Louis XIV., was composed chiefly of lead acetate.

shows that white lead and other insoluble preparations may act as violent and even fatal irritant poisons. When the acetate is ingested in toxic dose, the first symptom is usually a persistent, sweet, somewhat metallic taste; this in a few minutes is followed by vomiting, which may or may not be preceded by nausea. The matters vomited are often milky white, from the presence of lead chloride. A severe burning persistent pain in the abdomen now comes on, and is accompanied by a craving for drink. There may be obstinate constipation, or diarrhœa may ensue: in either case the stools are generally black from the sulphuret of lead. In certain cases a state of collapse is developed; the pulse falls to forty or fifty per minute, the voice is lost, the face is deadly pale, the lips are livid, and syncope seems imminent. In other instances the nervous symptoms may predominate, or they may accompany those of disordered circulation: cramps in the calves of the legs, severe neuralgic pains in the extremities, paralysis and anesthesia, vertigo, stupor, may any or all of them be present. In fatal cases, coma, with or without convulsions, finally develops. A distinctive mark of lead-poisoning, which occasionally is present very early, is the blue line upon the gums. After death inflammation of the alimentary mucous membrane is sometimes, but not always, found. One ounce of lead acetate, subacetate, or nitrate may take life.

The *treatment of acute lead-poisoning* consists in the evacuation of the stomach, the exhibition of sodium or magnesium sulphate, and the meeting of the indications as they arise. The Epsom and Glauber's salts act as chemical antidotes, by precipitating the insoluble sulphate of lead, and also, if in excess, empty the bowel of the compound formed. To allay the gastro-intestinal irritation, albuminous drinks should be given and opium freely exhibited.

*Chronic Lead-poisoning.*—Chronic lead-poisoning, or saturnism, is almost always accidental, and occurs most frequently among those whose occupation exposes them to daily contact with some compound of the metal; manufacturers of white lead, painters, glaziers, and similar artisans furnish the greater number of victims. It may be seen, however, in persons of all conditions of life, for although neither food nor drink is often purposely adulterated with lead, yet it is frequently introduced into the system accidentally along with those necessities. Lead pipes are habitually used for the conveyance of water, and when the water contains salts of lime, even in minute proportion, no evil results, because through the decomposition which ensues insoluble coatings are deposited on the inside of the pipes.\* When the water is pure, no such reactions occurring, the lead is slowly dissolved in the form of a carbonate, and poisoning may result. Poisoning has also frequently resulted from the employment of cosmetics and hair-dyes, from the internal or external medical use of lead preparations, from cooking bread with painted wood, from imperfectly

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\* For an elaborate article on the chemical relation of water to lead, see *Schmidt's Jahrbücher*, cxliv. 279.



burnt pottery, from habitually biting silk thread which rascally manufacturers often load with lead to give weight to it,\* from lead bullets retained in the body (Vucetiô), and from diachylon used as an abortifacient (Ransom), etc.

Two types of saturnism are recognized. The first in which colic is the most decided symptom is often spoken of as *subacute*. After some days of malaise and wretchedness, or sometimes very suddenly, the victim is taken with abdominal colicky pains, which increase in intensity until they become very severe. They are constant, with occasional exacerbations, are sometimes dull, sometimes sharp, are generally described as twisting, and seem to centre around the umbilicus. Very often there are repeated retching and vomiting. The walls of the abdomen are retracted, rigid, knotted; the bowels are obstinately costive; the tongue is contracted and whitish, the appetite gone, and the thirst sometimes excessive. Neuralgic pains in the thorax and in the extremities are of frequent occurrence. In some cases the conjunctiva is distinctly icteroid. This condition, which is known as *colica pictorum*, or *lead colic*, may after a time abate, and the patient convalesce; more usually, however, the attacks recur from time to time, becoming gradually less severe and distinctive, and the patient gradually passes into chronic lead-poisoning. Occasionally the colic increases in severity; sometimes the course of the disease is interrupted by various violent accidents.

In the second form of chronic lead-poisoning the abdominal symptoms may or may not be present, but the most marked features are referred to other organs, more commonly to the nervous system. The manifestations of lead intoxication, may, however, vary so much in their symptomatology as almost to baffle concise description. It has seemed to us that the symptoms can best be studied by arranging the cases in groups, but it must be remembered that in nature not only do these groups shade into one another, but also that there are all kinds of mixed cases,—cases which offer simultaneously or successively symptoms of two or more of these various groups.

The first group contains the great bulk of cases of chronic lead-poisoning, at least as seen in this country. The symptoms consist of failure of health, more or less digestive disturbance, and double wrist-drop,—i.e., paralysis of the extensor muscles of each hand. Not rarely, the only noticeable symptom is the wrist-drop, the general health seeming to be very good. The true nature of such cases can usually be at once recognized by the bilateral character of the wrist-drop, cerebral and pressure paralyzes being almost invariably unilateral. We have seen, however, bilateral pressure palsy, and also one or two cases of unilateral plumbic wrist-drop, due to a local absorption of lead, in artisans who had one hand much of the time in a preparation of the metal. Similar cases have been recorded by Manouvriez.†

\* Chronic lead-poisoning is produced much more frequently by insoluble than by soluble compounds of lead, but it is probable that any saturnine preparation may cause it. Thus, *lead chromate* has killed numbers of people. (See *Med. News*, ii. 1887; also *Therap. Gaz.*, iv.)

† See also *La France Méd.*, 1882, i. 829.

The wrist-drop may exist alone, but not rarely there is with it anesthesia of the affected part, or sometimes of the shoulders or other unparalyzed portion of the body. When the paralysis is complete, the electro-contractility of the muscles is in great part or altogether absent.

The rarer forms of chronic lead-poisoning may be divided into the cerebral, the periphoro-spinal, and the nutritive. In the cerebral cases should be included those which are commonly spoken of as *encephalopathia saturnina*, or *saturnine cerebritis*.\*

In cerebral cases of lead-poisoning the violent brain symptoms may develop with great suddenness, or may be preceded by some days of headache, giddiness, sleeplessness, disturbed vision, strabismus, tinnitus aurium, psychical aberration, or other prodromes of brain disturbance. Delirium, which is among the chief manifestations of the fully formed condition, may be mild, but is often maniacal; stupor may replace or alternate with it; and violent epileptiform convulsions, ending in coma, are not infrequent. These convulsions are usually the precursors of death, but recovery may occur even after the most severe symptoms.

Without the development of such severe symptoms, headache, loss of memory, giddiness, somnolence, hemianesthesia, disturbance of the special senses, aphasia, monoplegia, hemiplegia, or multiple cerebral palsies may occur during chronic lead-poisoning. Death, preceded by severe cerebral symptoms, may take place without organic lesion; but usually, when focal symptoms have been present, localized alteration of brain structure, secondary to diseases of the cerebral vessels, or to chronic inflammation of the brain or its membranes, can be detected. Sometimes the cerebral symptoms are uremic; indeed, true plumbic encephalopathy and plumbic uremia from contracted kidney may coexist. Again, the more serious affection may be masked by a saturnine hysteria, since cases have been reported by Charcot and by Dutil in which hysterical hemianesthesia, amaurosis, anosmia, loss of sense of taste, and other cerebral symptoms have been the outcome of a major hysteria due to chronic lead-poisoning. Such cases as these probably occur only in individuals of previously hysterical temperament, and must be extremely rare in persons not of the so-called Latin race.

Disturbances of vision are so frequent and so marked in lead-poisoning as to deserve special mention. They have been classified by De Schweinitz as follows:

1. Transient amblyopia, without ophthalmoscopic change.
2. Amblyopia without fundus lesions, or with congestion of the nerve-head, and with central scotomas analogous to those caused by other toxic agents.
3. Optic neuritis, or neuro-retinitis, either specifically due to lead or secondary to changes in the brain or kidneys.
4. Optic nerve atrophy, either consecutive to a plumbic papillitis or retrobulbar neuritis, or due to a primary effect of the lead on the visual organ.
5. Various types of retinitis, vasculitis, and perivasculitis, either primarily due to lead or secondary to nephritis.

Strabismus from muscular paralysis is sometimes of saturnine origin.†

The second group of cases of chronic lead-poisoning consists of those in which the nerve-symptoms apparently originate below the cerebrum.

In the present group belong cases such as have been reported by Putnam, by Tisier, by Raymond, and by G. L. Walton, in which the phenomena resemble those of locomotor ataxia, except in the presence of tenderness over the nerve-trunks,

\* George F. Crooke reports a case in which lead plaster taken for the production of abortion caused not only miscarriage, but also fatal brain lesions, preceded by choked disks, albuminuria, and convulsions.

† For discussion of details, see Manouvriez (*Arch. de Physiol. Norm. et Patholog.*, 1870, 411, 1876, 762), A. De Cours (*De l'Hémianesthésia saturnine*, Paris, 1875), Proust (*Progrès Méd.*, 1879; vii. 546), and Alex. Westphal (*Archiv für Psychiat.*, 1887-88, xix.).

preservation of the tendon reflexes, or some other atypical symptoms. We have seen several cases in which the symptoms resembled those of an acute poliomyelitis, consisting chiefly of wide-spread paralyses with rapid wasting of the muscles. These cases usually can be differentiated by the presence of violent neuralgic pains, paralysis of the bladder and rectum, or other atypical symptoms. Similar to these cases are those spoken of by G. Lyon, in which a rapid general paralysis spread from part to part, until at last aphonia and dyspnoea, and even death from asphyxia, resulted. Severe intractable chorea has been produced by lead. Oscar Buber calls attention to the form of irregular lead palsy in which the paralyzed muscles are affected with peculiar slow, worm-like, and occasionally painful contractions. Disturbances of sensation may occur in lead-poisoning; anesthasias are, perhaps, not very rare, and violent neuralgic pains, probably due to neuritis, may be the chief manifestation. In a case of H. C. Wood's in which the diagnosis was confirmed by finding lead in the drinking-water and in the urine of the patient, the symptoms were intense general pruritus, with violent neuralgic pains shooting through the rectum and the urethra, coming on at night and producing an insomnia which appeared to be unconquerable. The lesion is often peripheral, and the very rapid pulse seen in some cases may be due to disease of the vagi, which Prevost and Binet have found degenerated.

The third group of cases comprises those in which the poison chiefly expends itself upon glandular or visceral organs, or in producing wide-spread nutritive changes.

It would seem that almost any of the vital structures may undergo degeneration. Potain reports a case of saturnine cirrhosis of the liver; while Valence and Claisse and Dupré call attention to plumbic parotiditis, which may take the form of a slowly progressive chronic hypertrophy of the gland, with dryness of the mouth, or of a distinct sclerosis, or there may be ulceration of the orifice of Steno's duct and obstruction. Rudolf Maier has found in poisoned animals atrophic degenerations of the intestinal glands and walls. Sailor found in twelve cases of saturnism a constant reduction in the secretion of hydrochloric acid.

Of great frequency and importance are the lesions produced by lead in the kidneys. It must be remembered that temporary albuminuria may occur in lead-poisoning without serious implication of the kidneys; while, on the other hand, fatal nephritis may exist when there is no albumin in the urine (Lancéreaux). A persistent low specific gravity of the urine in lead-poisoning is a symptom of the utmost gravity. Geppert confirms the observation, previously made by Olivier, that in temporary plumbic albuminuria many isolated kidney epithelial cells may often be found in the urinary sediments; and it is evident that a persistence of this condition must end in chronic renal disease. After death, which may be induced by uremia, the kidneys are found contracted, granular, with excessive development of the fibrous tissue (followed by contraction) and great thickening of the walls of the blood-vessels; these changes are identical with those of contracted kidney produced by gouty and other irritant poisons. As Ellenberger and Hofmeister have shown that the lead is chiefly eliminated by the kidneys, the frequency of plumbic nephritis is easily explained; but it is not readily perceived why it is so frequently associated with an arthralgia whose course and lesions closely simulate those of chronic gout. Garrod (1859), Dickinson, Lancéreaux, Rosenstein, Leyden, and other authors have reported so many cases of this association of renal and gouty manifestations that it can scarcely be doubted that the plumbism is the cause of the gouty symptoms, and not simply a complication of gout.\*

There are certain cases of lead-poisoning which do not conform to any of the types as yet given.

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\* Consult *Deutsch. Med. Wochenschrift*, 1883, 185, 351; 1884, 129; also Paul Musehold (*Die Bleivergiftung*, Berlin, 1883). We have ourselves seen one case.



Among these very irregular cases may be mentioned those reported by E. Levy, in which acute asthma was produced by the inhalation of the dust of white lead. Again, chronic saturnine asthma is sometimes seen in feeble, narrow-chested people. James J. Putnam calls attention to the fact that in lead-poisoning of children the legs and feet are commonly paralyzed. Pagliano has reported a case of saturnine facial palsy. It has been abundantly proved both by clinical experience and by experiments made upon the lower animals that in chronic lead-poisoning the metal may pass through the placenta into the fetus, causing its death, with subsequent abortion.\*

As any of the obscure manifestations of lead-poisoning may exist, and even prove fatal, without a distinct history of other more characteristic phenomena, great care is sometimes necessary to avoid being misled, and not rarely the true nature of saturnine epilepsy or of saturnine albuminuria is overlooked. Hence the importance of the *blue line upon the gums where they join the teeth*, which is very common in persons suffering from lead-poisoning. It is said to be the result of a formation of lead sulphide in the walls of the capillaries. As was first pointed out by J. J. Putnam, chronic lead-poisoning may exist without this blue line upon the gums. Under such circumstances, if the symptoms be obscure the diagnosis can be established only through a chemical examination of the urine.† The practitioner should see that the urine which is to be sent to the chemist for examination be slightly acidified, that directly after passing it be put in flint-glass bottles, and that it be at least a quart in quantity. From a diagnostic point of view an extremely important observation, if it be confirmed, is that of Deroide and Lecompt, who assert that there is in the urine of saturnine patients *urohematoporphyrine*, a red pigment, soluble in ether, water, and alcohol, which can readily be recognized by the spectroscope.

In those cases of lead-poisoning which pursue a slow course to death the paralysis involves after a time the extensors of the lower as well as of the upper extremities, epileptic paroxysms occur at intervals, racking pains shoot through the limbs, points of cutaneous anesthesia appear, and often albuminuria aids in producing the fatal issue. Gradually the patient becomes more and more cachectic, general œdema and the whitened skin betray the increasing anemia, the paralysis extends from muscle to muscle, locomotion becomes impossible, and, if a convulsion or other accident do not close the scene, death at last takes place from loss of power in the respiratory muscles.

Plumbic anemia is probably due, at least in part, to a direct action of the lead upon the blood or the blood-making organs. According to Malassez, the red blood-corpuscles during the anemias are not only diminished in number, but also increased in size. Sabrazes and Bourret have found in the blood of a case of serious acute lead-poisoning normoblasts, basophilic, granular, and polychromatic cells, also

\* See Constantine Paul (*Archiv Gén.*, 1860, xv.), Legrand and Winter (*Compt.-Rend. Soc. Biolog.*, 1889), and B. Annino (*Schmidt's Jahrb.*, cexliv., No. 11).

† For an elaborate discussion, see leading article in *Therap. Gaz.*, Dec. 1887; *Ibid.*, iii. 813, and iv. 92.

neutrophilic, polymorphonuclear leucocytes. In chronic lead-poisoning, Moritz found granulation of the basophilic erythrocytes, and was able to produce such a change in lower animals.

After death lead has frequently been detected in almost all of the tissues.

Heubel found most of it in the bones, and less in the muscular than in the nervous system. Chatin obtained from the cervical spinal cord three in one hundred and fifty parts. In the studies of Ellenberger and V. Hofmeister the liver and kidneys were found to contain the most lead, after them the bones, then the nerve-centres, and finally the flesh. Prevost and Binet found the lead in all the tissues, but believe that it especially accumulates in the kidneys.\* G. N. Pitt reports finding over forty-seven grains of the lead sulphide in nine inches of the colon.

The electro-muscular contractility is affected very early in lead-poisoning, and may be lost before the voluntary movements. It is stated by M. Raymond that the short extensor of the thumb preserves its function when all the other extensor muscles are paralyzed. The paralyzed muscles are finally exceedingly wasted, and their structure may be so totally destroyed that scarcely a single striated fibre can be found. The nerve-trunks are lessened in size, in many of their tubules the medulla has been replaced by fatty granules, and in some cases every trace of the tubules has disappeared and the nerve has been reduced to a fibrous cord.

According to the researches of Dégérine, the first appearance of change in a nerve-trunk consists in the myeline becoming broken up into blocks, and the nature of the change is a commingling of a parenchymatous and an interstitial neuritis, which both Dégérine and Vulpian have traced upward as far as the anterior spinal roots. Lancéreaux, Westphal, Friedländer, and others may be cited as having found very distinct peripheral lesions in lead-poisoning. Whether these lesions begin in the nerve or in the muscles cannot be considered as determined. Birdsall reported a case of what he believed to be a plumbic myositis, and Goubault describes primary alteration in the nerves, similar to those seen after section, as occurring in poisoned guinea-pigs, while Debove and Reaut describe the first changes as resembling those of subacute myositis, and Friedländer emphatically asserts that lessening in the size of the muscular fibres and multiplication of the muscular nuclei

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\* A question of the most serious importance, which at present we are not able to answer positively, is as to whether sclerosis, neuritis, and other chronic affections of the nervous system which have been reckoned as idiopathic or of unknown origin are not frequently the outcome of an entirely latent lead-poisoning. In a remarkable paper, J. J. Putnam, of Boston (*Trans. Assoc. American Physicians*, ii.), describes cases entirely apart from recognized types of lead-poisoning, in which the metal was found in the urine. These cases may be grouped as follows: 1. Trembling of hands; sense of coldness and numbness in toes; lancinating pains in legs; fatigue on exertion. 2. Marked progressive spastic paraplegia, with myosis and pupillary reactions; ataxia and some atrophy of hands. 3. Progressive weakness and stiffness in legs, with diffused and almost universal pains; marked tremor. 4. Temporary pain in chest, with slight dyspnoea; progressive numbness, heaviness, and weakness in legs. 5. Numbness in feet and legs, with impairment of strength; tremor of hands and tongue; some wasting of small muscles of hands; temporary retention of urine. Closely connected with this subject is the question whether lead may not be for a length of time in the system and appear in the urine without doing injury to the health. In a paper (*Boston Med. and Surg. Journ.*, 1890, cxxiii.) Putnam brings forward more facts, whose import is at present very doubtful. In an examination of the urine of sixty-eight persons, presenting no evidences of any disarrangement of health, lead was found in the proportion of about seventeen per cent., while the urine of thirty-six persons suffering from chronic and subchronic affection of the nerves, nerve-centres, and spinal cord contained lead in the proportion of fifty per cent. In the last group were cases of tremors with debility, of chronic multiple neuritis, multiple sclerosis, spastic paraplegia, muscular atrophy, epilepsy, sciatica, digestive disorders, etc. (*Bost. Med. and Surg. Journ.*, 1889, cxi.). One cannot help suspecting that, owing to defective water-supply, Bostonians are especially prone to contain lead. For a minute description of various forms of lead palsy, see *Le Saturnisme*, Meillère, Paris, 1903.

precede the nerve-degeneration. On the other hand, Vulpian, Monakow, Oeller, and a number of other observers\* have noticed structural changes (poliomyelitis, capillary hemorrhages, etc.) in the spinal cord of men dead of plumbism; while Popow found that when guinea-pigs were rapidly poisoned (six to eight days) with lead there was produced a central myelitis, which first affected the large cells of the gray matter, and afterwards involved the white matter, the peripheral nerve-filaments remaining normal. There is, however, no real contradiction, as Popow believes, between his observations and those of Goubault, for the latter poisoned his animals very slowly (six months), and it is not improbable that the rapidity of the poisoning had an influence upon the seat of the lesion. As already stated, the symptoms of plumbism may exactly simulate those of general poliomyelitis, and both Dégérine and Leopold Stieglitz found degeneration of the motor cells. Karl Schaffer believes that two sharply separated forms of degeneration of the nerve-centres occur in chronic lead-poisoning,—one consisting of a minutely granular destruction of the protoplasm, the other of the homogenization of the contents of the cell.

The evidence at present indicates that lead is capable of producing a peripheral neuritis, and also a centric poliomyelitis, which may or may not coexist in an individual case; the probabilities being in favor of a peculiar peripheral neuritis, as the primary lesion of ordinary plumbic wrist-drop (see paper by Schultze, also Prevost and Binet). Hemorrhages into the nerve-centres sometimes occur.† There seems to be no doubt that lead really affects the nutrition of almost all of the higher tissues. In saturnine encephalopathy changes have been found in the ganglionic cells as well as in the neuroglia, with stenosis of capillaries and general shrinkage of the cortex (see O'Carroll). Marked alterations are not rare in the kidneys and other glandular organs, and general fibrosis of the blood-vessels is probably more or less developed in every slowly fatal case of chronic poisoning (case, Fisher).

The *excretion* of lead with the gall is very active, but it is probable that it chiefly escapes from the body with the urine. The elimination seems to be capricious, and much affected by potassium iodide and by other influences. (See Melsens, Annuschat and Pouchet.)

The *treatment* of chronic lead-poisoning evidently arranges itself under three indications: first, to prevent the ingestion of more of the poison; second, to aid in the elimination of that in the system; third, to relieve symptoms and restore lost functions. In lead colic the last two indications are met by purgatives, to which opium should be added to relieve pain. It is often necessary to use the most powerful drastics, such as croton oil; but senna, salts, and other of the milder cathartics should always be tried first. *Alum*, it is asserted, acts in some unknown way as a specific in lead colic, and from twenty to sixty grains of it may be given four or five times a day; but our experience is not favorable to its use. In the more chronic forms of lead-poisoning, to fulfil the second indication baths of potassium sulphuret should be employed, and potassium iodide be administered

\* For references, see *Arch. f. Psychiat. und Nervenkr.*, xvi. 447.

† See *Prog. M.*, xii. 827.



internally.\* As the result of special investigation, Oddo and Silbert conclude that the elimination of lead through the skin in chronic lead-poisoning is important, that it is facilitated by injections of pilocarpine, and that the sulphur baths are valuable in the treatment of chronic lead-poisoning. The bath should be given (A. Eulenburg) in a wooden tub, two or three times a week, and should contain six or seven ounces of the salt. The patient, during the half-hour of his continuance in it, from time to time should be well rubbed with a coarse towel. On coming out he is to be thoroughly washed with warm soapsuds. The dose of the iodide should be from fifteen to twenty grains, administered after meals, in dilute solution. A case is reported† in which galvanic baths were used successfully, the patient being placed in the bath and the positive pole of a twenty-eight-cell battery applied to the nape of the neck, the negative to the feet. When severe cerebral symptoms arise, treatment is of little avail, and should be largely expectant. In cases of lead-poisoning in which the symptoms resemble those of acute poliomyelitis we have used ascending doses of strychnine with most extraordinary results, rapidly deepening paralysis being almost at once controlled. It is essential that the strychnine be pushed to the point of systemic intolerance. It is best to administer it by the mouth, or if used hypodermically it should be given at least twice a day. It may possibly prove of value in other acute forms of lead palsy.

The local use of electricity is exceedingly important to restore the lost function of nerve and muscle. When the faradic current elicits a response, it should always be employed; but in some cases the continued current retains its power after the induced has lost all its influence. The rule is always to apply that current which causes contraction; if both fail, the continued current should be used, the poles being reversed at intervals of four or five seconds. The electrical sésances should be triweekly, each lasting about fifteen minutes, and they should be persevered in for months. We have seen great improvement in a case which for the first four months yielded no results; indeed, long after voluntary movement had in great measure returned, no form of electricity would cause contraction of the affected muscles.

**Physiological Action.**—The symptoms of acute lead-poisoning are chiefly due to its local irritant action, but those of chronic poison-

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\* As the result of a careful series of analyses, J. D. Mann (*Brit. Med. Journ.*, 1893, i.) concludes that in chronic lead-poisoning there is a great fluctuation in the elimination of lead, that potassium iodide has no real effect in increasing the elimination, that lead is eliminated from the intestines even more freely than from the urine, and that the previous contrary results obtained by investigators have been due to chance coincidences of the iodide treatment with increase of the lead excretions from other cause. He recommends especially *general massage*, and confirms to some extent the assertion of Tedeschi, that this massage increases remarkably lead elimination. On the other hand, cases are reported in which lead was not in the urine before, and was after the administration of the drug (see *Brit. Med. Journ.*, 1880, ii. 1034). Moreover, John Marshall (*Therap. Gaz.*, iv. 97) has shown by actual experiment that potassium iodide in solution has an action on the insoluble lead carbonate and phosphate, with the formation of a soluble lead compound,—double lead and potassium iodide; and therefore, if lead taken into the system be deposited in the tissues as insoluble carbonate or phosphate, these latter compounds, on the administration of potassium iodide, will be decomposed, with the production of a soluble lead compound, and consequently a more rapid elimination of the lead will occur.

† *L. L.*, 1876, ii. 53.

ing are of wider significance. How the lead is absorbed to produce them is uncertain, — probably as an albuminate. All the compounds of lead and albumin as yet discovered by the chemist are, however, precipitated by alkaline carbonates, and cannot, therefore, exist in the blood.

The symptoms of chronic lead-poisoning are probably in great part secondary to the structural alteration produced by the drug, lead being a poison to all forms of protoplasm. Why in one case one set of organs should be attacked and in another case a different portion of the body is a mystery. The nephritis which is so common a result is no doubt connected with the effort to eliminate the poison from the system.

The chief research we know upon the effects of lead upon the lower animals is that of Ernest Harnack, who employed the compound of lead and ethyl first discovered by Loewig. When this is injected into animals in large quantities it causes a rapidly fatal train of symptoms evidently due to the action of the compound itself. When, however, the introduction into the system has been slow, a chronic poisoning is produced by the lead set free in the blood and tissues.

Under these circumstances a constant symptom in both dogs and rabbits is diarrhoea, due to a violently increased peristalsis, with, in the dog, occasional attacks of colic. Harnack found that in dogs the lead ethyl produces violent excitement, with chorea, convulsions, etc., evidently due to an exciting or irritant action upon the cerebrum, and believes that this explains the saturnine cerebral cases sometimes seen in man.

The chief symptom of the poisoning in frogs was a progressive palsy of muscular origin. The muscle became exhausted on repeated galvanization much more rapidly than is normal, and after death was incapable of undergoing complete post-mortem rigidity. The peripheral nerves appeared to have escaped entirely. The heart-muscle shared the fate of the voluntary muscles. The muscular action of the poison was excessively pronounced in rabbits, but was feeble in dogs and cats. Different results have, however, been arrived at by H. von Wyss, who found that the loss of reflex activity, etc., in the frog was not prevented by tying an artery so as to protect the leg from the poison, and that the protected muscle lost its power of responding to electrical stimulation just as fast as did the one reached by the lead. He concludes, therefore, that the paralysis is of centric origin. Curci is stated to have proved that lead exerts an irritant influence upon the peripheral branches and ganglionic centres of the pneumogastric. According to the researches of Ellenberger and Hofmeister, in the sheep toxic doses of lead greatly depress the elimination of urea.

The pulse in lead colic is usually very hard and tense. Sphygmographic studies made of it by August Frank and Ernest Bardenhewer have been thought to indicate a condition of general arterial spasm, and have given rise to the theory that the colic is caused by intestinal anemia from vaso-motor contraction. Harnack, however, found that in dogs and rabbits the lead ethyl has no action upon the vaso-motor system and does not produce spasm of the vessels. Moreover, he determined that both the diarrhoea and excessive peristalsis produced in dogs were arrested by atropine, which ought to promote rather than lessen vaso-motor contraction. Lead colic in man is probably due to

a spasmodic contraction of the intestines so powerful as to arrest peristalsis, and to so press upon the blood-vessels as to force the blood from the abdomen into the general circulation.\*

### BISMUTH.

Metallic bismuth is not used in medicine. Of the six official salts the citrate is not itself used except in the form of bismuth ammonium citrate, which differs from the other official preparations of bismuth in being soluble in water. It occurs in small shining translucent scales with a metallic taste. The insoluble salts of bismuth are all of them heavy, odorless, tasteless powders, the subnitrate and subsalicylate being white, the subgallate bright yellow and the subcarbonate pale yellow. The subnitrate of bismuth frequently contains free acid and should, therefore, not be prescribed with the alkaline carbonates. The subcarbonate on the other hand is decomposed by acids.

There is no evidence that there is any essential difference between the therapeutic effects of any of the insoluble official salts of bismuth, nor that any of the various new chemical compounds of this metal have any advantage over the official preparations.

#### Official Preparations:

Bismuthi Citras.....	Not used internally.
Bismuthi et Ammonii Citras.....	2 to 5 grains (0.13-0.3 Gm.).
Bismuthi Subcarbonas.....	5 to 60 grains (0.3-4.0 Gm.).
Bismuthi Subgallas.....	5 to 30 grains (0.3-2.0 Gm.).
Bismuthi Subnitras.....	5 to 60 grains (0.3-4.0 Gm.).
Bismuthi Subsali-cylas.....	5 to 30 grains (0.3-2.0 Gm.).

**Physiological Action.**—The insolubility of the ordinary salts of bismuth makes their absorption so slow that in the ordinary methods of administration they have practically no effect upon the system. Under certain conditions, however, they may be absorbed in large enough quantities to give toxic effects (see p. 305).

It was formerly believed that the insoluble salts of bismuth were not dissolved at all in the alimentary canal, but it is now certain that they are very slowly absorbed and as slowly eliminated. Harnack affirms that the metal has been found by Orfila in the liver, spleen, and urine, and by Lewald in the milk. Bergeret and Mayençon state that when bismuth subnitrate is administered the metal can always be detected, after a few hours, in the urine. They have also discovered it in the serous exudation of dropsy, and have proved that when a few grains of the salt mentioned are given to rabbits, in from twenty to thirty minutes it can be found in the urine, kidneys, spleen, blood, and muscles, and even eight days after the administration can be detected in all the tissues. Five days after the exhibition of a gramme

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\* Bardenheuer affirms that pilocarpine given hypodermically will relieve simultaneously the pulse and the colic.



of the subnitrate to a man they found traces of the metal in the liver and kidneys; but the analysis of the body of a woman dead sixty-two days after the ingestion of two grammes yielded negative results. E. S. Wood also has detected bismuth in the urine four weeks after its last exhibition.

According to Feder-Meyer the bismuth and ammonium citrate causes in rabbits violent tremblings with diarrhœa, accompanied after large doses by disturbance of the sensibility and of coördination, tetanic cramps, altered respiration (in the beginning accelerated and superficial, afterwards becoming slow), continual lowering of the blood-pressure, and death. The same observer noticed in chronic poisoning similar symptoms with albuminous urine and after death fatty degeneration of the liver, heart, and renal secreting structure. Similar observations were made by Mory, who states that the death in mammals is the result of cardiac paralysis, and that in the advanced stages of chronic poisoning, when the blood-pressure is very low, it is not elevated by stimulation of the splanchnic nerves nor by asphyxia. W. Steinfeld has obtained in the frog from the administration of bismuth ammonio-citrate and ammonio-tartrate peculiar tremblings of the voluntary muscles with prolongation of contraction upon stimulation with the galvanic current, and slowing of the heart's beat, also after sufficient doses paralysis of nerves and muscles; effects which he attributes not to the bismuth, but to the acids of the preparations. He states that the proper symptoms produced by the metal appear only after some hours, and consist of motor excitement with reflex cries which are due to irritation of the medulla oblongata. In acutely poisoned mammals he noticed vomiting and purging, convulsions with loss of power, slowing of the pulse, and sinking of the blood-pressure, believed by him to be all of centric origin. In chronic poisoning there was loss of certainty of movement with cardiac depression followed by increasing paralysis, usually ending in death without convulsions. In his studies upon absorption and elimination he found that the ammonio-citrates and ammonio-tartrates are quickly eliminated through the kidneys, so that, as a rule, after from ten to fifteen hours they can no longer be found in the blood, tissues, or urine.

The discovery by Theodore Kocher that the most insoluble bismuth preparations are actively antiseptic led to their use in surgery, and to the further discovery that when applied in very large quantities to extensive wounded surfaces they are capable of yielding so much bismuth to absorption as to produce a poisoning, which is characterized by acute stomatitis, sometimes gangrenous, with a peculiar black discoloration of the mucous membrane, usually beginning upon the borders of the teeth, but spreading over the whole mouth, followed by an intestinal catarrh with pain and diarrhœa, and in severe cases with desquamative nephritis, as shown by albuminous urine and epithelial tube-casts.\*

Bennecke reports a case of bismuth-poisoning, ending fatally, in a feeble infant to whom between three and four grammes had been given for skiagraphic purposes. Methemoglobin was found at the autopsy.

That bismuth is capable of acting as a poison in the lower animals has been abundantly proved by the experiments of F. Balzer and of P. Dalché and E. Villejean, which show that, whether given by the mouth or hypodermically, repeated large doses of it produce gradual failure of strength, a peculiar stomatitis, and evi-

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\* For cases, see Kocher, also Petersen (*Deutsches Med. Wochenschr.*, June 20, 1883).

dences of gastro-intestinal irritation, with death from exhaustion. Balzer states that the stomatitis which it causes differs from the stomatitis of pytalism in the tendency to rapid gangrenous change; and also that the bismuth is eliminated with the saliva, bile, and urine, but has a distinct tendency to accumulate in the tissues.

**Therapeutics.**—It is stated that after the administration of bismuth it may be demonstrated (by means of the Roentgen rays in the living animal, and by means of the microscope in animals killed) that the insoluble preparations of bismuth gradually spread themselves over the gastro-intestinal mucous membrane, and undergo a slow conversion into the black oxide of bismuth.\* Experimental science, therefore, is in accord with the conclusion previously reached by clinicians, that by virtue of their physical and chemical properties these bismuth preparations act as protectives to the mucous membrane, and especially by their slow change and absorption not only exert an antiseptic influence, but have a peculiar persistent sedative, astringent action. They are, therefore, of great service in the treatment of irritations and inflammations of those mucous membranes with which they can be brought in contact. Thus, they are useful to allay *vomiting* dependent upon gastric irritation. In simple neuralgic *gastric pain* following eating, especially when occurring in feeble, badly nourished subjects, bismuth is often of great service; and even in *carcinoma* it may palliate by alleviating pain and vomiting. In *pyrosis* it is sometimes successful; in *gastric* and *enteric catarrhs* it is a standard remedy. In the simple *diarrhæa* of irritation and in the *chronic diarrhæa* of camps the bismuth preparations are often very efficient; and in the chronic *bowel complaints* of children, especially as seen in the summer season, given with pepsin, they are almost invaluable. Bismuth is a very serviceable topical remedy in the treatment of mucous inflammations and of ulcers to which it can be applied directly. Thus, in the beginning of a *gonorrhæa*, the injection every two hours of a mixture containing thirty grains of bismuth to the ounce usually brings immediate relief; in a similar way it may be employed in *leucorrhæa* and in *acute coryza*. In Germany it has been to some extent used as a surgical dressing.

**Administration.**—In order to get the best attainable results from the use of bismuth subnitrate it is necessary to vary the dose and method of administration. In stomachic affections from five to fifteen grains (0.3–1 Gm.) may be given preferably when the stomach is empty, in order that the bismuth may be distributed as closely as possible over the gastric mucous membrane. In intestinal diseases from fifteen grains to a drachm (1–4 Gm.) may be exhibited in capsule from one to two hours after meals at a time when the gastric contents are escaping through the pylorus. Children bear proportionately very large doses: thus, five to ten grains (0.3–0.6 Gm.) may be given to a two-year-old infant.

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\* Consult *Centralblatt f. innere Medizin*, 1894, S. 2.

The ammonio-citrate of bismuth in small dose is actively stimulant, astringent, and, probably, germicidal. In large dose it is a violent irritant. It has none of the peculiar properties which grow out of the insolubility of the subnitrate, but is more astringent, and has been used in *chronic diarrhæa* and in the *acute diarrhæas of relaxation*.

BISMUTH OXYIODOGALLATE or *Airol* is a grayish-green, non-irritating, tasteless, odorless powder, containing about two parts of bismuth to one part of iodine. When brought in contact with a surgical surface it turns red from the liberation of iodine. According to the studies of Carl S. Haegler it is in its bactericidal properties about equivalent to iodoform, the products of its surgical decomposition being, as in the case of that drug, active germicides. Injected into the lower animals in doses of from one to three grammes per kilo, it causes clonic convulsions, with coma, nephritis and fatty degeneration of the liver. Theoretically the toxic dose should produce the combined symptoms of iodine- and bismuth-poisoning, but in Haegler's experiments the symptoms rather resembled those caused by bismuth, and in a case reported by Aemmer, symptoms of bismuth-poisoning followed the injection into the cavity of an abscess of nine and one-half fluidrachms of the ten per cent. glycerin solution. Haegler took fifteen grains of airol in the course of three days without the production of any disagreeable symptoms. It has been largely used as a substitute for iodoform on account of its lack of odor. It may be employed for the making of antiseptic gauze or similar dressings, or applied directly as a dry powder; as a salve of ten to twenty per cent. with lard or vaseline free from water, or be injected in ten-per-cent. glycerin solution in *tubercular* or other *abscesses*, or used in the form of suppositories made with cacao-butter in *metritis*, *vaginitis*, etc. *Brun's paste*, much used in various skin diseases and ulcerations, consists of airol one part, mucilage and glycerin each two parts, kaolin sufficient to make a soft paste.

### CERIUM OXALATE.

*Cerium oxalate* of the U. S. Pharmacopœia is a white powder, insoluble in water, alcohol, and ether, but soluble in hot diluted hydrochloric or sulphuric acid. It is a mixture of the oxalates of cerium, didymium, præsodymium, lanthanum, and other rare earths. It has been employed in medicine quite largely for the relief of *vomiting*, especially when dependent upon *pregnancy* or other forms of *uterine disturbance*. Its action on the economy has not yet been made out, but it may be tried with some hope of success in cases of nervous or dyspeptic vomiting. The dose is one to three grains (0.06–0.2 Gm.), in pill, three or four times a day.

### ZINC.

The salts of zinc are astringent and antiseptic. They have some action, not clearly defined, upon the system after absorption. Chronic zinc-poisoning, if it really exists at all, is very rare, and the metal seems to be used with impunity in cooking-utensils.

Schlockow affirms that zinc-smelters rarely live to be over forty-five years of age, dying sometimes of catarrh of the bronchial or alimentary mucous membranes, or, in other cases, of a peculiar nervous affection, which commences with



burning superficial pains, exalted sensibility and reflex activity in the legs, and afterwards puts on still more clearly the features of myelitis; and A. Sacher finds that intravenous injection of very large doses of zinc salts produces paralysis of the voluntary muscles.

#### Official Preparations:

Zincum.....	Not used internally.
Zinci Acetas.....	2 grains (0.12 Gm.).
Zinci Bromidum.....	2 grains (0.12 Gm.).
Zinci Carbonas Precipitatus.....	External use.
Zinci Chloridum.....	External use.
Zinci Iodidum.....	1 grain (0.06 Gm.).
Zinci Oxidum.....	2 grains (0.12 Gm.).
Zinci Phenolsulphonas.....	2 grains (0.12 Gm.).
Zinci Stearas.....	External use.
Zinci Sulphas.....	As an emetic 15 to 30 grains (1-2 Gm.).
Zinci Valeras.....	3 grains (0.2 Gm.).
Unguentum Zinci Oxidi (20 per cent.).....	External use.
Unguentum Zinci Stearatis (50 per cent.).....	External use.
Liquor Zinci Chloridi (50 per cent.)	Not used internally.

**ZINC SULPHATE.**—*White Vitriol* occurs in irregular white masses, the *pure* zinc sulphate in minute, transparent, four-sided, prismatic crystals, which effloresce slightly in dry air, and are soluble in 0.53 part of water at 77° F. and in 0.2 part of boiling water, also soluble in about three parts of glycerin; insoluble in alcohol. The taste is styptic and peculiar.

Zinc sulphate is, in weak solution, a stimulant astringent; in concentrated form an active irritant. Its chief value is as a rapidly acting emetic, especially in cases of poisoning. Dose, thirty grains (2 Gm.). In doses of one grain (0.06 Gm.), it has been given in pills as a stimulant astringent in *chronic diarrhœa* with ulceration.

**Toxicology.**—Zinc sulphate in large doses acts as an irritant poison, producing violent vomiting, colicky pains, diarrhœa, prostration, etc. The symptoms which it causes are almost identical with those produced by the corresponding salt of copper. Alkalies and their carbonates are the chemical antidotes to it, producing insoluble precipitates. Eggs and milk should also be exhibited, and the symptoms treated as they arise.

**ZINC OXIDE.**—*Commercial zinc oxide* is a snow-white powder, obtained by burning the metal in the air. It should be used only in pharmacy. The pure oxide is a white or yellowish-white powder, insoluble in water or alcohol, but soluble without effervescence in dilute acids.

**Therapeutics.**—Zinc oxide is used externally as a mildly astringent, slightly stimulant, and desiccant application in *skin diseases* and to *ulcers*. When given continuously in small doses it is believed to act as a tonic and alterative upon the nervous system. It has also been commended as an astringent in chronic *catarrhal diarrhœa* of adults

and infants, and has been largely used in *epilepsy* and in *chorea*. Dose, one-half to two grains (0.03–0.13 Gm.). The ointment is useful in various *skin diseases*.

**ZINC CARBONATE.**—*Hydrated zinc carbonate* is intended to replace the old impure native carbonate, *calamine*. It is made by precipitating the zinc sulphate by the sodium carbonate. It is a white powder, closely resembling in its medical properties zinc oxide.

**ZINC ACETATE.**—*Zinc acetate* occurs in white, micaceous crystals, which effloresce in a dry atmosphere and are very soluble in water. The taste is astringent and metallic. The zinc acetate resembles in its physiological and therapeutic qualities the sulphate, but is probably somewhat less active. It is chiefly used in collyria (one to two grains to one fluidounce), and as an injection (one to twenty grains to one fluidounce) in *gonorrhœa*.

**ZINC BROMIDE.**—This is a white or nearly white deliquescent powder of a saline metallic taste. In full doses it is an irritant emetic but has been chiefly used in *epilepsy*. Its value is doubtful.

**ZINC CHLORIDE.**—Zinc chloride occurs in white or nearly white porcelain-like masses freely soluble in water. It is used as a caustic and disinfectant.

**ZINC IODIDE.**—A white or nearly white deliquescent powder which deserves no place in the U. S. Pharmacopœia.

**ZINC PHENOLSULPHONATE.**—The sulphocarbolate of zinc occurs as efflorescent, colorless crystals, freely soluble in water. It is largely used as an intestinal antiseptic but is probably of no value.

**ZINC STEARATE.**—This is a white powder with a slight fatty odor, insoluble in water, alcohol, or ether. It is used as a dusting powder in similar conditions to those calling for zinc oxide.

## COPPER.

The only official salt of copper is the sulphate. This occurs in blue, transparent, slightly efflorescent, rhomboidal prisms, or their fragments. It dissolves, at 77° F., in about 2.2 parts of water and in 0.5 part of boiling water; almost insoluble in alcohol. With ammonia its solution precipitates a bluish-white cupric hydrate, which redissolves when an excess of the alkali is added, forming a rich deep blue solution.

**Physiological Action.**—In very dilute solution the copper sulphate acts locally as a stimulant and mild astringent; in a more concentrated form it is an irritant; in powder it is a very mild caustic, which is scarcely capable of destroying sound tissue. The salts of copper in sufficient amount are poisonous to all forms of protoplasm. Coupin found that 0.0055-per-cent. solution of soluble salt of copper will prevent germination of wheat; that copper compounds affect violently the general nutrition in animals is shown by the production of fatty degeneration by them (see Ellenberger and Hofmeister).

According to Falck, the cupric sulphate causes in the lower animals great depression of temperature, with progressive general paresis, ending in death, apparently from failure of respiration. When the copper salt was given hypodermically, vomiting was not produced; although when it was exhibited by the mouth, emesis was very violent and persistent.

Cupri Sulphas..... $\frac{1}{4}$  to  $\frac{1}{2}$  grain (0.008–0.015 Gm.);  
as an emetic 3 to 5 grains (0.2–0.3 Gm.).

**Therapeutics.**—Cupric sulphate is occasionally used for its local effect in chronic *enteritis* and *colitis*, with ulceration, but is rarely of value. It was at one time much employed in the treatment of organic nervous diseases, but has fallen into deserved desuetude. Forty years ago Mendini recommended it in the treatment of *chlorosis* with amenorrhœa, a use which has been revived from time to time and has recently been commended by Liégeois. A. F. Price claims that cupric sulphate in doses of one-thirtieth of a grain three times a day greatly enhances the power of the mercurials in syphilis.

The chief value of the so-called *blue stone* is as an external application. When applied in solid form to ulcers, it destroys flabby granulations and exerts a powerful excitant influence. Its solution acts more feebly, and is sometimes employed as a dressing for indolent *ulcers*, but more frequently as a stimulant and alterant to mucous membranes, as in *granular conjunctivitis* and *urethritis*.

In 1904 Moore and Kellerman of the U. S. Department of Agriculture stated that copper sulphate even in minute quantities is capable of destroying both algæ and typhoid bacilli. According to Gildersleeve 1 part in 1,000,000 is sufficient to kill all typhoid germs in water in three hours although other microorganisms seem more resistant. This property depends probably on the dissociation of the ions, for metallic copper seems to be more efficient than any of its salts. Stewart found that water inoculated with typhoid bacilli and kept in copper vessels contained none of these organisms after three hours and comparatively few of the other forms of bacteria, and Kraemer has shown that copper foil placed in the water has the same effect. It does not seem probable that the minute quantity of copper present in these circumstances (about 1 part to 4,000,000) can exercise any very deleterious effect on the system, especially as much of it becomes united with the organic matters and precipitated. When large amounts of foreign substances are present in the water copper is so much less efficient in its germicidal powers, that according to both Fowler and Doty it is of no practical value.

**Toxicology.**—The symptoms of acute copper-poisoning generally come on in about a quarter of an hour, but may be postponed for from one to two hours. They consist of violent vomiting and purging, accompanied by the very severe colicky pains. The matters vomited are greenish or bluish, the stools glairy, mucous, and at times bloody. There is a very strong taste of copper in the mouth,



and often constant expectoration; excessive salivation and bronchial secretion are stated by Galippe to be characteristic. Death may occur in a few hours, preceded by convulsions, paralysis, delirium, anesthesia, and other symptoms of great nervous disturbance, seemingly as the result of a direct action of the poison upon the nervous system. Sometimes a tendency to syncope is very marked, and as both L. Schwarz and W. Filehne have found that toxic doses of copper salts paralyze the heart in the lower animals, cardiac death probably occurs in human poisoning. The urine is usually lessened or suppressed. Black urine, due to the presence of hemoglobin without unaltered blood-corpuscles, has been noted; in this case, after death all the tissues were found stained with altered blood, and evidently destruction of the blood was an important factor in the fatal result;\* fatty degeneration of the liver was also found. If the patient survives for twenty-four hours, jaundice nearly always shows itself. After this, profound depression with nervous symptoms may develop and end in death; but not rarely a favorable issue results, in which case the symptoms of gastro-intestinal inflammation with fever develop themselves. The copper is said to be eliminated more freely with the salivary and intestinal secretions than with the urine (Galippe).

As the action of the cupric sulphate is exceedingly rapid, any antidote to be of avail must be given at once and act quickly. In the poisoning milk, eggs, or other albuminous substance should be exhibited immediately, freely, and repeatedly.† Soap or a fixed alkali may be used. The yellow *prussiate of potash*, when pure, is harmless, and precipitates instantly an insoluble compound of copper from solutions of its salt. When it is to be had in time, it may therefore be used as an antidote to the sulphate. The treatment of copper-poisoning after the administration of the antidote consists in meeting the indications as they arise; opium should be used freely. When death occurs, the results of gastro-intestinal inflammation are usually found; sometimes the intestine has a decided bluish tint, and occasionally submucous ecchymoses occur. In exceptional cases, it is said, there are no evidences of inflammation in the alimentary canal.‡ Fatty degeneration of the liver has been noted in man.

There has been much discussion as to whether there is or is not a chronic copper-poisoning among workers in that metal.

The chief symptoms which have been described as present are coppery taste in the mouth, gastro-intestinal irritation with pain, anemia, progressive emaciation, cough, and nervous disturbances with tremors. The green discoloration upon

\* N. Y. M. R., xxi. 567.

† No time should be lost in attempting to separate the yolk from the white of the egg, but the egg should be broken into a bowl as quickly as possible, a little water added, and the whole stirred up and exhibited.

‡ For a fatal case of repeated poisoning by copper, with much information of value to chemical experts, see *La France Méd.*, September, 1874, abstracted in *Half-Yearly Compendium*, January, 1875. Bourneville and Yvon (*Revue Scientifique*, 1874, 859) found two hundred and ninety-five milligrammes of metallic copper in the liver of a woman who had taken the ammoniacal sulphate three months previously. Minute quantities of copper exist in the normal human body (*Bull. Thérap.*, xciii. 88).

the gums or teeth, which was first pointed out by Clapton, has been noted by Taylor, by the Committee of the London Clinical Society, and various other observers. It is, however, not constant, and may exist in persons who show no other evidences of poisoning. According to Kurth, it really consists of a greenish or olive discoloration on the front of the teeth, and is due to the staining of the tartar, since when the teeth are perfectly clean there is no staining. It is probable that most, if not all, of the symptoms of the chronic poisoning noted in workers in copper are due to the local action of the copper dust upon the various mucous membranes, an explanation which is rendered more probable by the fact pointed out by Kurth, and also by Lewin, that workers in copper often have their hair colored green.

When copper is given to the lower animals in continuous sufficient dose it produces loss of appetite, failure of digestion, diarrhœa, and other evidences of gastro-intestinal catarrh; with marked evidences of disturbances of the nutrition, such as emaciation, failure of the heart, and with a progressive paralysis and failing respiration ending in death. After death alterations of the blood and wide-spread fatty degeneration have been noted by numerous observers.\* According to Von Bókay the muscles are very early affected, cloudiness of their protoplasm and disappearance of their cross-striation coming on. The liver and kidneys, however, are especially attacked: in the beginning there are hyperplasia of the connective tissue and subacute nephritis, followed by fatty degeneration and finally atrophy.

Although Galippe and Burcy and also Ducom affirm that copper is almost without influence upon dogs, and Galippe fed himself for one month on food containing a large amount of copper without causing any symptoms of intoxication, it is probable that while very minute quantities of copper may be taken internally habitually without producing injury, larger doses may slowly and insidiously work out fatal consequences. The matter is important because the metal is habitually used in the canning of vegetables, French peas, beans, etc., owing their attractive color to their treatment with copper, which can be chemically recognized in them.

The possibility of injury from such food has been repeatedly investigated by French and Belgian commissions, and the general verdict has been that no harm is produced. The fact that twenty millions of cans of these food-articles are consumed every year, and that after thirty-six years' continuance of the custom it has not been clearly established that harm is done, indicates that in the amount used the vegetables containing copper are not poisonous. It is plain that the freedom from injury depends upon the minuteness of the amount of copper ingested; the Italian law does not allow more than 0.05 gramme of copper per kilo of food, but the researches of Tschirch would indicate that a food containing this amount of copper, if very freely taken, might do harm.†

### SILVER.

Probably all the salts of silver are more or less actively germicidal (see page 655) in their influence as well as astringent. Three salts of silver are recognized by the Pharmacopœia: the cyanide, the nitrate and the oxide.

*Silver cyanide* is used only for the manufacture of hydrocyanic acid; never as an internal remedy.

\* Falck (*Deutsch. Klinik*, 1859, xi.), Ellenberger and Von Hofmeister (*Arch. Wissen. Prakt. Thierheilk.*, x, 228), W. Filehne (*Deutsch. Med. Wochen.*, 1893, xxi.), De Moor, Von Bókay (*Pester Med.-Chir. Presse*, 1897, 33), Baum and Seeliger (*Archiv f. Thierheilk.*, 1897, xxiii., 1898, xxiv.), and Trolldenier (*Archiv f. Thierheilk.*, 1897, xxiii.).

† For discussion upon the subject, see De Moor (*Archives de Pharmacodynamie*, 1895, i.) and Tschirch (*Toxicologie und Hygiene*, Stuttgart, 1893).

*Silver oxide* is a dark brown powder almost insoluble in water and readily reduced by the action of light to metallic silver. It is comparatively little used.

*Silver nitrate* exists in translucent shining rhombic crystals with a styptic metallic, corrosive taste. It is freely soluble in water, and moderately soluble in alcohol. For external use the crystals are melted and run into moulds, where they harden into round, grayish, brittle sticks, about the size of a goose-quill, and having a radiated crystalline fracture. These constitute the official ARGENTI NITRAS FUSUS. As only the pure salt will make well-formed crystals, the impure products are always manufactured into the fused nitrate, which should therefore not be employed internally. When silver nitrate, either in substance or in solution, is exposed to the conjoint influence of light and of even a minute portion of organic matter, it turns black, and is converted into an insoluble substance, which has been believed to be metallic silver, but is more probably an oxide. For this reason the white stains which it first makes when applied to living tissues soon blacken.

**Official Preparations:**

Argenti Cyanidum.....	Not used internally.
Argenti Nitras.....	$\frac{1}{4}$ grain (0.015 Gm.).
Argenti Nitras Fusus.....	External use only.
Argenti Nitras Mitigatus.....	External use only.
Argenti Oxidum.....	1 grain (0.06 Gm.).

**Physiological Action.**—*Local Action.*—Silver nitrate coagulates albumin, and, when applied in its pure state to living tissues, acts as a caustic, coating them over with a white almost membranous film. The caustic action is, however, not a deep one, because penetration of the salt into the tissues is soon prevented by the thick and tough skin or stratum which is formed. When applied in a dilute solution it acts as an astringent, constricting the vessels and overcoming relaxation. Its local action, however, is not simply that of an astringent, but is certainly peculiar and apparently alterative to nutrition. It is also a very active germicide.

*Absorption and Elimination.*—It is evident that in the stomach silver nitrate cannot long maintain its integrity. Bogolowsky has found that when the nitrate is added to a peptone it is readily dissolved, and that the solution formed does not coagulate albumin.\* That in this or in some other analogous form silver is absorbed is proved by its having been found in various internal organs and by the discoloration which follows its protracted use: *argyria* of authors. When it is exhibited for a long continuous period, the skin often acquires a peculiar bluish slate color, which may become very dark, and in decided cases the conjunctiva and even the mucous membrane of the mouth are involved. The silver is found in all the tissues of

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\* For recent studies of this character, see Isidore Neumann (*loc. cit.*), also A. von Fragstein (*Berlin. Klin. Wochen.*, 1877, 294).



the skin below the rete Malpighii\* (Frommann, Riemer, Neumann). E. Harnack asserts that in all recorded cases of argyria at least thirty grammes of the salt have been taken. The staining of the skin is always preceded by a dark discoloration of the mucous membrane of the mouth and gums. Both Heller and Orfila failed to detect silver in the urine of animals taking it; but probably it is eliminated, though slowly and in very small quantities, by the kidneys.

*General Effects.*—As silver is never given for an immediate therapeutic action, its acute physiological action is of less interest to the therapist than to the toxicologist, and the detailed symptoms of its poisoning are considered under the head of toxicology. In general these symptoms consist of those of gastro-enteritis with violent disturbance of the nervous system, due to a direct action of the poison upon the cerebrum and the spinal cord.† Although the circulation is profoundly affected, death appears to take place from centric paralysis of respiration.

By an elaborate series of experiments Charles Rouget has shown that upon all animals from a crab to a dog the soluble salts of silver act as a poison, causing in mammals vomiting and purging, and in them and the lower animals violent disturbance of the motor functions, as shown by paralysis and convulsions, and of the respiration, ending finally in death by asphyxia. This is in accord with the observations of other investigators. Rabuteau and Mourier affirm that the almost instantaneous death which Charcot and Ball first noted, as following the injection of a large dose of silver nitrate into the veins, is due to a direct paralyzing influence of the drug upon the muscle of the heart. Rouget has never seen this form of death follow the hypodermic or internal administration of the poison, the heart always continuing to beat for a greater or less length of time after the cessation of respiration, and also retaining its irritability.

As already stated, both convulsions and paralysis are present in acute silver-poisoning. The convulsions are severe, generally tetanic, and according to Rouget are plainly reflex. A peculiarity noted by Rouget is the persistence of the convulsions after the complete abolition of voluntary movements. Curci affirms that they are due to excitation of the motor tract of the cord, and that this is preceded by a similar influence upon the sensory tracts.

The death is due, in argyria, to cessation of the respiration; Rouget even states that he has witnessed the suspension of the latter function in the frog while the activity of the reflex movements was much beyond normal. In the dog and in the full-grown cat this asphyxia is accompanied by an outpouring of mucus in the lungs, pulmonary congestion and oedema being found on post-mortem examination. Two theories have been propounded as to the cause of the asphyxia: one, that it is simply due to the choking up of the lungs by the congestion and the excessive secretion whose origin is an altered state of the blood; a second, that both the asphyxia and the lesions in the lungs have their origin in a direct action of the poison upon the nerve-centres.

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\* In an elaborate study of the organs of a case of argyria, Riemer detected the silver in the glomerules of the kidney, the intima of the aorta, the choroid plexus, and the mesenteric glands. He believes that it is never deposited inside the cells, and that the silver preparation is reduced in the intestines, and the fine particles of the silver carried in the blood and lymph. Gerschun (*Arbeiten aus Physiolog. Inst. zu Dorpat*, x.) coincides with Riemer in affirming that the silver is deposited outside of the cells, but O. Loew (*Pflüger's Archiv*, xxxiv. 603) asserts that it occurs inside of the renal endothelial cells. Jahn (*Beiträge z. Patholog. Anat.*, xvi.) states that the unstriated muscular fibres and the elastic tissue have a special power of reducing silver.

† Orfila and other of the earlier observers experimented upon it by injecting it directly into the veins of animals. When exhibited in this way, it must, by coagulating the albumin of the blood, produce thrombi, to which the subsequent symptoms are in greater or less measure to be ascribed. This method of experimentation can, therefore, throw but little light upon the action of silver nitrate when taken into the stomach.

The first view has been especially supported by Krahmer and by Rabuteau and Mourier. Unfortunately, we have not seen the original papers of these physicians; but, according to Rouget, the basis of the argument of Krahmer is simply the ecchymoses which he found in horses dead of the poison, while that of Rabuteau and Mourier is the fluidity of the blood after death, and the existence in it of granules which, on account of their solubility in ammonia, were believed to be silver chloride. The French observers were, however, almost certainly mistaken in their belief that these granules were silver chloride, since ammonia dissolves hematin as freely as it does the chloride.

In 1864 Charcot and Ball made a series of experiments in which a silver salt that did not coagulate albumin was injected directly into the blood. They noted not only the respiratory embarrassment, but also that the hinder extremities were suddenly paralyzed, and concluded that both the asphyxia and the lung trouble were due to an affection of the central nervous system. In 1869 Bogolowsky, of Moscow, studied the action of a peptone of the nitrate when used hypodermically. He found, on examination of the blood of a poisoned animal, that the spectrum analysis betrayed nothing abnormal; that the red corpuscles appeared paler and their outline more delicate than normal; and that the white corpuscles were natural. On the other hand, Rouget examined microscopically the blood of animals poisoned with silver nitrate, and found it perfectly normal. The only conclusion to be drawn from all this seems to us to be that at present there is no proof whatever that the symptoms of acute silver-poisoning are due to alterations in the blood; that the embarrassment of respiration is not due to local lesions in the lungs is abundantly shown by the experiments of Rouget, who found that while in all animals these respiratory symptoms are very prominent, in only a few species are decided pulmonary lesions found after death. From all these facts we think it highly probable, if not altogether certain, that the theory propounded by Charcot and Ball is correct. That the motor disturbance is centric, not peripheral, in its origin, is shown by the fact noted by Rouget, that the muscles and nerves preserve their excitability after the arrest of the respiration.

We know of very few, if any, cases of chronic poisoning with silver salts in man (see foot-note, page 318); the following summary epitomizes the results of chronic poisoning in the lower animals.

The action of the drug when exhibited continuously for a length of time in large doses has been investigated by Bogolowsky upon dogs and rabbits. He found that it produced loss of appetite, wasting, slight lowering of bodily temperature, diarrhoea, diminution of the quantity of urine passed, with increase of its specific gravity and often with the presence of albumin, and transitory paralysis. How far some of these symptoms were due to the direct constitutional action of the poison and how far to derangement of the digestion dependent upon its local influence is perhaps an open question. The local action was avoided, however, as much as possible, by the use of an albuminate or of the double phosphate of silver and sodium, which does not coagulate albumin. Comparative examinations of the blood showed that the hemoglobin was diminished by more than one-third. The blood was also rendered very aplastic, as was betrayed by the constant tendency to the formation of ecchymoses. As some one has suggested that the silver in these cases replaces the iron of the blood-corpuscles, Bogolowsky made a chemical examination of the latter, but failed to find any traces of silver in them,—no doubt because it was not there. The solid tissues were found, after death from chronic argyria, to be in an advanced stage of degeneration, which especially affected epithelial structures. The first change was swelling and opacity of the cells, with obscuration of the nucleus. After this came fatty degeneration, fatty globules in the cell, destruction of nucleus, and finally of the cell itself. The liver and kidneys were profoundly influenced, as was also the muscular structure, especially of the heart. These results obtained by Bogolowsky have been in the main corroborated by A. V. Rózsahegzi.

**Therapeutics.**—The results of the chronic poisoning by silver are in every way so closely analogous to those produced by antimony, arsenic, copper, and other metallic poisons as to show that silver belongs to that class of drugs which in some way markedly affects the general nutrition. It cannot, however, be called an alterative, as at present we know of no application of its power to the needs of practical medicine.

The only advantageous use of silver in therapeutics is for its local action either upon the surface of the body or upon those mucous membranes that can be reached directly by the drug.

As a simple *caustic*, the salt may be used whenever a superficial action only is required: for reasons already given (page 313), it is useless whenever it is necessary to produce a deep eschar. As a *caustic alterative*, it is applied in solid form to many *ulcerated surfaces*, for the purpose of destroying superficial diseased tissue and of substituting, when the eschar separates, a healthy for an unhealthy action. As an antiphlogistic, silver nitrate acts not only as an astringent, but also as a germicide. In the various inflammations of the mucous membranes, such as *conjunctivitis*, *faucitis*, *laryngitis*, *urethritis*, etc., it is used very frequently, not only in the stage of relaxation, but also in the beginning of the attack. In *conjunctivitis*, the solution employed should not, under ordinary circumstances, be stronger than one or two grains to the ounce; and it should not be used at all if any corneal ulceration exists, since a deposit of silver is liable to occur and to produce opacity. In *faucitis*, the strength of the solution may vary from thirty to sixty grains to the fluidounce. In ordinary cases of *sore throat*, the application once a day or every alternate day is generally sufficient. It is best made by means of a good-sized camel's-hair brush, each part of the inflamed surface being distinctly touched, and not the whole simply daubed or slopped over by means of a very large brush or a sponge probang. In severe cases it may be necessary to use the solution twice a day. Even a saturated solution can scarcely be looked upon as caustic to the more robust mucous membranes.

Carl Seiler states that while solutions of silver nitrate of less than sixty grains to the ounce cause pain when applied to the throat, solutions of one hundred and twenty to two hundred and fifty grains act as local anesthetics, relieving soreness, and usually arresting acute inflammations at once, if applied in the first twenty-four hours, before inflammatory exudation has occurred.

In *laryngitis*, the solution may contain from ten to twenty grains to the ounce, and should be applied with a brush by the aid of the laryngoscopic mirror. An attack of *urethritis* may sometimes be aborted in its forming stage by the injection of a strong solution (twelve grains to one fluidounce) of the salt; but the practice is of doubtful expediency, since when it fails it greatly aggravates the trouble. When *chronic gonorrhœa* is strictly localized to a small spot in the posterior urethra, instillation of from five to ten minims of



a solution of the strength of five to ten grains to the fluidounce is often serviceable. When the inflammation is more diffused, irrigation with a weaker solution is preferable; at first 1 to 5000 may be employed, and the strength gradually increased to even 1 to 500.

Applied to the skin of the whole finger, silver nitrate will sometimes abort a commencing *felon*, or, applied to the scrotum, an *epididymitis*.

Internally, silver nitrate is exceedingly useful in stomachic and to a less extent in enteric diseases, exerting no doubt a purely local influence. In that form of *dyspepsia* characterized by the vomiting of large quantities of yeasty fluid, it has yielded in our hands better results than any other remedy; and the same may be said of *chronic gastritis* and of *gastric ulcer*. The rules of administration are identical in these three diseases. In the first place, regulation of the diet is imperative: if the case be a bad one, all eating of meals should be suspended, and the patient receive every two or three hours a cup of sweet milk, with sound toasted bread broken up and thoroughly softened in it. In order to wash off as much as possible the mucous membrane of the stomach, and to neutralize the acids of the stomach, forty-five minutes before the meal fifteen to twenty grains of sodium bicarbonate should be exhibited in a tumblerful of hot water, and ten minutes later a quarter of a grain of silver nitrate should be given in pill form. The use of cold water at meals should be absolutely forbidden, and in very serious cases, when all food is rejected by the stomach, it is sometimes advisable to allow absolute rest for two or three days to that viscus, the patient being fed by the rectum, and only a little water and pills of silver with opium being taken by the mouth. Under these circumstances, the return to the usual method of taking food must be very gradual, at first only a tablespoonful each of milk and of lime-water being administered every hour. In *chronic enteritis* or *colitis*, silver nitrate is sometimes of service, especially if there be ulceration.

For its constitutional effects silver nitrate is used solely in diseases of the nervous system. It was formerly given in *epilepsy*, but it has passed out of use. In *chronic inflammations* of the spinal cord, whether affecting chiefly the posterior columns and constituting *locomotor ataxia*, or the anterior and giving rise to *paraplegia*, it is still employed, but is of doubtful value.

**Toxicology.**—The symptoms produced by the ingestion of large doses of silver nitrate are partly gastro-intestinal and partly cerebrospinal. In some instances the one series of phenomena predominate, in others those of the other class. In a case\* at the Hôpital St.-Louis in 1839 the symptoms were insensibility, violent convulsions, dilated pupils, and, when consciousness was partially regained, intense gastric pain: complete restoration of consciousness did not occur until eleven hours after admission, and the coma returned at intervals during several days.

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\* Beck's *Medical Jurisprudence*, 1863, i. 675.

Vertigo, coma, convulsions, great muscular weakness, and paralysis, with intense disturbance of respiration, are in these cases the manifestations of disturbed innervation, while the abdominal symptoms are those of gastro-enteritis. The diagnosis can generally be made by the discolorations of the lips and skin—at first white, afterwards black—and by the blackish or brownish vomit; when the customary antidote has been given, both vomit and stools are generally white and curdy. After death the stomach and bowels are found corroded, often ecchymosed and with patches of a white or grayish color. Poisoning by silver nitrate is not common, and we know of but three fatal cases,—one in 1837 (Taylor), one in 1861, a woman killed by fifty grains in solution in divided doses, and one in 1871, a child destroyed by a piece of the solid stick three-quarters of an inch long, in spite of the use of the antidote (Scattergood).

The treatment consists in the administration at once of large amounts of *common salt*, alkaline carbonates, or soap,—the chemical antidotes,—the constant use of large draughts of milk, and the meeting of symptoms as they arise.

The fatal dose of silver varies very much, according, no doubt, to the presence of substances capable of decomposing it in the stomach. Thirty grains have killed, and recovery has taken place after the ingestion of an ounce (case, Husemann).

Chronic *argyria*, or discoloration of the skin by silver, is usually unaccompanied by disturbances of health, although in severe cases the discoloration affects not only the skin, lips, gums, and sclerotic, but even the internal organs, such as the liver, spleen, and kidneys. It is therefore not due, as has been thought, to the silver chloride, since the latter becomes dark only under the influence of the light, but to a deposition of silver itself or of its oxide.\*

S. Krýsinski found the granules in almost every tissue of the body, and states that they are an organic compound of silver, the exact nature of which has not yet been determined. The minute quantity of the metal present is shown by the analysis of Versmanns, who in 14.1 grammes of dried liver found only 0.0068 gramme of metallic silver (0.047 per cent.), and in 8.6 grammes of dried kidney 0.053 gramme (0.61 per cent.). Greater or less success has been asserted for various treatments in argyria, but in general they are equally futile.

Rogers states that blistering will lighten the color very much, and Eichmann asserts (Husemann) that he has cured two cases by the use of potash baths and of soap baths, each four times a week. The older authorities commend the use of potassium iodide internally. L. P. Yandell has reported two cases in which large doses of the iodide were given for many months for syphilis, and the mercurial vapor-baths used at the same time for the same purpose, with the result of a complete cure of the argyria. The fading was gradual.

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\* According to Rózsahégzi, Hermann has seen one case in which preceding the deposition of the silver there were malaise, emaciation, failure of memory, ringing in the ears, deafness, and spasms of the ocular muscles.

**Administration.**—The silver nitrate should always be given in pill, and, when it is desired to obtain its constitutional influence, after meals, during the process of digestion; but when its local action on the stomach is required, it should be administered one or two hours before meals; and if the intestines are to be reached, the pill should be enclosed in two thick capsules. The administration of silver nitrate should not extend over a longer time than two months without a protracted intermission.

**ALBARGIN. Gelatose Silver.**—This compound of silver and gelatose is a yellowish, bulky powder, dissolving readily in cold or warm water, and containing fifteen per cent. of silver. It affects albumin slowly, but may be used with cocaine provided the double solution be freshly prepared at the time of administration. It should be kept in amber-colored bottles. It was introduced by Bornemann, to be used in a one- to two-per-cent. aqueous solution in *gonorrhæa*.

**SILVER ACETATE.**—This has been especially recommended by Zweifel in a one-per-cent. solution for the treatment of *ophthalmia* in new-born children.

**SILVER CITRATE. Itrol.**—A dry, odorless powder, soluble with difficulty in water, has been recommended as intensely poisonous to the gonococcus and non-irritant to the urethral membrane. The injection of from 1:4000 to 1:8000 solution is said to produce no pain even in acute *gonorrhæa*, and may be practised four times a day. The remedy has also been used in *chronic cystitis*.

**SILVER LACTATE. Actol.**—This substance is soluble in fifteen parts of water, and may be used in very strong or saturated solution for the disinfection of infected wounds. It is decomposed at the point of application, but is said to form soluble compounds, so that it is able to find its way deeply into the tissues. One gramme has been given hypodermically without serious symptoms, except some burning. The application of the pure powder to an affected surface is asserted to produce only moderate and brief pain.

**ARGENTOL.**—A yellowish powder which readily splits up into oxyquinoline and metallic silver; it has been recommended by Cipriani as efficient, in *diarrhæa*, as an astringent, intestinal antiseptic of which fifteen grains (1 Gm.) may be given safely in twenty-four hours, if necessary. It has also been used surgically in the strength of 1 to 300 to 1000.

**ARGYROL. Silver Vitellin.**—This albuminous compound of silver occurs in dark-brown hygroscopic scales, very freely soluble in water, and containing about thirty per cent. of silver. It has been largely used, but both Derby and Marshall and Neave have found that it possesses no germicidal properties.

**LARGIN.**—This compound of silver and albumin is a whitish-gray powder, soluble to about ten per cent. in water, freely soluble in blood serum, not precipitated by albumin, and containing 11.1 per cent. of silver. It has great penetrating power when brought in contact with tissue, and has been highly praised by a number of German clinicians as a germicide in the treatment of *gonorrhæa* both in men and women. It is used in strengths of one-fourth to four or five per cent. In infectious *conjunctivitis* and in *catarrhal corneal ulcers*, Welander especially commends the use of gelatin tablets containing one per cent. of largin.

**SILVER SULPHOCARBOLATE. Silberol.**—Introduced by Zanardi as a substitute for silver nitrate, this substance has been considerably used in *gonorrhæa*, and as a surgical germicide, especially in connection with the eye. It is asserted that the two-per-cent. solution is well borne by the conjunctiva, and that when used as a substitute for silver nitrate *silberol* must be employed in twice as concentrated a solution.



**SOLUBLE SILVER.** *Colloidal Silver. Collargol.*—This allotropic form of silver, discovered by M. Carey Lea in 1891, occurs as a bluish or green-colored mass. It makes with water a deep red solution, which is precipitated by the addition of salt solutions. Soluble silver was originally employed by Credé as a non-poisonous germicide, to be used for internal medication in various affections, such as *septicemia*, *diphtheria*, and *tuberculosis*. At first he exhibited it by inunctions, forty-five grains at one time for the adult, but later gave five to ten grammes of the one-per-cent. solution hypodermically or intravenously. The harmlessness of these intravenous injections has been confirmed by Müller, who also affirms that in *septic diseases* collargol may be given with as much trust as antitoxin in diphtheria. The value of the remedy is, however, very doubtful. The experiments of George Brunner have shown that collargol is precipitated by gelatin or bouillon; that it is not soluble in blood serum although it remains dissolved if the solution of it be mixed with the serum; that the germicidal properties of it are very feeble,—twelve hours' contact with the one-per-cent. solution of it being required to kill most pathogenetic bacteria; that when given subcutaneously or intravenously it has no apparent effect upon animals, and that granules of silver can be found later at the places of injection; finally, that whether given with infected matter or injected after the material, in the lower animals it has no influence over the processes of infection or upon the bactericidal power of the blood. The chills and other constitutional disturbances which were formerly produced by the intravenous injections of collargol were probably due to the presence of impurities in the solutions used, and the whole drift of present evidence is to show, that collargol probably never circulates in the blood to any extent, and that it is physiologically inert.

**ARGONIN.** *Silver Caseinate.*—An albuminous preparation of silver, readily soluble in warm or albuminous water, has been highly recommended in inflammations due to *gonococci*. Its ten-per-cent. solution is said to produce no pain; even in acute cases it may be used freely.

**ICHTHARGAN.** *Silver-thio-sulphonate.*—This compound of silver and ichthyol contains about thirty per cent. of silver and fifteen per cent. of sulphur. It is a brown amorphous powder, readily soluble in water, glycerin, and dilute alcohol, but insoluble in absolute alcohol; and is precipitated from its solution by sodium chloride and albumin; the latter precipitate, however, being redissolved by an excess of albumin. It is stated to add to its germicidal and antiphlogistic influences a distinct locally anesthetic power.

According to the researches of Aufrecht, ichthargan is much more destructive to gonorrhœal, pyogenic, diphtheritic and typhoid germs than is either colloidal silver or protargol, its one-per-cent. ointment being as active as the fifteen-per-cent. of collargol. According to H. C. Wood, Jr., this preparation does not differ essentially in its physiological action from the ordinary salts of silver. Both Aufrecht and Wood, Jr., have found that ichthargan is much less toxic than silver nitrate. The experiments of Derby as well as of Aufrecht indicate that ichthargan is even more actively germicidal than silver nitrate.

Ichthargan is being very largely used in gonococcal and other infective diseases of the mucous membranes; also in various infected ulcerations and skin diseases. It has been especially commended in various forms of *rhinitis*, *tonsillitis*, *laryngitis*, and other affections, chronic and acute, of the upper respiratory mucous membrane, either applied in spray of the glycerin solution varying from four to ten per cent., or less freely in solutions up to twenty per cent. The strength of the ichthargan solution varies in *gonorrhœa* from 1:500 to 1:3000 for injections; from 1:2000 to 1:5000 for irrigation; one to three per cent. in instillations. In *trachoma*, *gonorrhœal*, and other *infective conjunctivitis*, the one- to three-per-cent. solution may be applied with a brush; 1:1000 used as a wash. In *eczema*, *ulcerations*, *phlegmons*, *vaginitis*, and *lymphangitis*, the ointment, varying from one to fifteen per cent., is advised, well rubbed into the adjacent thoroughly cleansed healthy skin, and also applied directly to the affected surface if it be exposed.

Ichthargan has also been administered internally with asserted and excellent results for the relief of *gastritis*, and especially of *gastric ulcers*. Dose, one-twentieth to one-eighth of a grain in half an ounce of water on an empty stomach.

**PROTARGOL.**—The chemical combination of silver and protein occurs as a fine, yellowish powder, readily soluble in cold water. Its solution is precipitated by albumin, by dilute solutions of sodium chloride, or by dilute acids and alkalies. It is said to contain eight per cent. of metallic silver, and was originally proposed by Professor Niesser as having the antiseptic properties of the silver salts, and being able to penetrate tissues on account of its not coagulating albumin. According to the experiments of Petitjean, Athanasion, and Compareseo, the injection of protargol into the jugular vein of the dog produces in a very few minutes a fatal pulmonary œdema, probably due to deposition of silver and consequent mechanical obstruction. Protargol has been much used in *gonorrhœa*, *infective conjunctivitis* of various forms, as well as in *infected wounds*. In gonorrhœa it may be used in strengths varying from one-half to two per cent., according to the mode of employment. In infected wounds a lengthened application of the five-per-cent. solution may be made, or the powder itself used by dusting, or a ten-per-cent. ointment applied.

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## FAMILY II.—TONICS.

### IRON.

IRON is official in the U. S. Pharmacopœia in a metallic state, as well as in a large number of salts. The salts may be conveniently divided into two groups, the soluble and the insoluble. The soluble salts of iron may be further divided into two groups, those in which the base is combined with an inorganic acid and those containing an organic acid radical. The latter class include the various citrates and tartrates and are frequently spoken of as the "scale salts" of iron from the fact that they occur in thin transparent scales, mostly of a garnet-red color—except the iron and quinine citrate, which is greenish-yellow.

**Official Preparations:** (The important ones are marked with †.)

The soluble solid preparations of iron are as follows:

Ferri Chloridum (22 per cent.*)	1 grain (0.06 Gm.).
† Ferri Phosphas Solubilis (12 per cent.)	5 grains (0.3 Gm.).
Ferri Pyrophosphas Solubilis (10 per cent.)	5 grains (0.3 Gm.).
Ferri Sulphas (20 per cent.)	2 grains (0.13 Gm.).
Ferri Sulphas Exsiccatus	1 grain (0.06 Gm.).
Ferri Sulphas Granulatus	2 grains (0.13 Gm.).
Ferri et Ammonii Sulphas (11.5 per cent.)	5 grains (0.3 Gm.).
Ferri Citras (16 per cent.)	5 grains (0.3 Gm.).
† Ferri et Ammonii Citras (16 per cent.)	5 grains (0.3 Gm.).
Ferri et Ammonii Tartras (13 per cent.)	5 grains (0.3 Gm.).
† Ferri et Potassii Tartras (15 per cent.)	5 grains (0.3 Gm.).
Ferri et Quininæ Citras (13.5 per cent.)	5 grains (0.3 Gm.).
Ferri et Quininæ Citras Solubilis (13.5 per cent.)	5 grains (0.3 Gm.).
Ferri et Strychninæ Citras (16 per cent.)	2 grains (0.13 Gm.).

The insoluble solid preparations are:

Ferrum (Iron Wire)	Not used internally.
† Ferrum Reductum (90 per cent.)	2 to 5 grains (0.13–0.3 Gm.).
Ferri Carbonas Saccharatus	3 to 5 grains (0.2–0.3 Gm.).
† Massa Ferri Carbonatis [Vallet's Mass] (20 per cent.)	3 to 5 grains (0.2–0.3 Gm.).
† Pilulæ Ferri Carbonatis [Blaud's pills]	1 to 3 pills.
Ferri Hypophosphis (22 per cent.)	3 grains (0.2 Gm.).
Ferri Hydroxidum	$\frac{1}{2}$ to 1 ounce (15 to 30 Gm.).
† Ferri Hydroxidum cum Magnesii Oxido	$\frac{1}{2}$ to 4 fluidounces (15–120 C.c.).
Pilulæ Ferri Iodidi	2 pills.

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\* The percentages given refer to the proportion of metallic iron present.

The liquid preparations containing iron are:

Liquor Ferri Chloridi (10 per cent.)	3 to 5 minims (0.2–0.3 C.c.).
† Tinctura Ferri Chloridi (4.6 per cent.)	10 to 30 minims (0.6–2.0 C.c.).
† Liquor Ferri Subsulphatis (13.6 per cent.)	3 to 5 minims (0.2–0.3 C.c.).
Liquor Ferri Tersulphatis	To make the Hydroxide.
† Liquor Ferri et Ammonii Acetatis [Basham's Mixture]	4 fluidrachms (15 C.c.).
Glyceritum Ferri, Quininae et Strychninae Phosphatum	15 minims (1 C.c.).
Syrupus Ferri, Quininae, et Strychninae Phosphatum	1 fluidrachm (4 C.c.).
† Elixir Ferri, Quininae et Strychninae Phosphatum [Triple elixir]	1 fluidrachm (4 C.c.).
† Syrupus Ferri Iodidi	15 to 30 minims (1–2 C.c.).
† Mistura Ferri Composita [Griffith's mixture]	$\frac{1}{2}$ to 1 fluidounce (15–30 C.c.).
Vinum Ferri	2 fluidrachms (8 C.c.).
Vinum Ferri Amarum	2 fluidrachms (8 C.c.).

*Absorption.*—Iron is a constituent part of many tissues of the body, but is especially abundant in the red blood corpuscles. Among the older chemists Quevenne taught that the exhibition of the salts of iron had little influence upon the amount of iron in the urine. This fact was confirmed by Bunge and since then by numerous other chemists and gave rise to the belief by some that the ordinary salts of iron were not absorbed into the blood. This theory had at one time a large following and led to the manufacture of a large number of preparations in which iron was supposed to be present in the form more nearly resembling the combinations in which it was found normally in the body, and which are generally known as “organic salts” of iron. In the light of more recent investigations, however, there appears no longer to be any room for doubt that the Pharmacopœial salts of iron are absorbed from the intestinal tract, nor does there appear any good reason to believe that the so-called organic preparations of iron have any advantage over the older combinations of this metal.

The most important arguments which were advanced against the absorbability of inorganic iron through the intestinal tracts are: First, that the quantity of iron in the urine is not notably increased after the administration of iron by the mouth; second, that the amount of iron in the urine is increased after the hypodermic administration of iron; third, that the system requires extremely small quantities of iron, not over 10 milligrammes a day for the ordinary man. These facts have been so abundantly confirmed that they do not permit of contradiction, but, on the other hand, the conclusions drawn from them are not logically justified.

To the first reason may be answered that absence of urinary elimination is not proof of non-absorption; it is perfectly conceivable that other organs, especially the intestinal tract, might eliminate the iron from the system, or that it might be stored up for considerable periods of time in the system. Experimentation has shown that this is the real explanation of the failure to find iron in the urine. Thus Gottlieb obtained, after the hypodermic administration of iron, nearly ninety-seven per cent. of the injected iron from the feces, while Gottlieb, Jacobi, and Zaleski, all present evidence to show that iron is stored up in the liver. To the second argument, while it is true that the quantity of iron in the urine is increased after the hypodermic administration, the amount which passes out through the kidney is much smaller than that which is eliminated by the intestinal tract. The third

argument advanced against the absorption of iron presupposes that the inorganic salts of iron act upon the system as foods, which is probably not the case.

On the other hand, there is to-day abundant evidence, of a direct nature, that iron is absorbed from the intestinal tract.

Kunkel for eight weeks fed two dogs upon milk, giving to one of them iron in addition, and bleeding each dog equally from time to time. After the killing of the dogs the blood and the various organs of the body were carefully analyzed, and it was found that iron was in distinct excess in all the organs of the dog to which the metal had been given, and that in the blood there was one and a half times as much of the iron, and in the liver eight times as much, as in the similar tissues or organs of the dog used for control. Justus Gaule detected chemically iron in the lymph coming from the thoracic duct of a rabbit into whose stomach a dilute solution of the ferric chloride had been injected. Quinke not only proved that iron is excreted from the mucous membrane of the large intestine, but also that absorbed iron can be detected in the walls of the duodenum, a fact which has been confirmed by Hall, by A. Hoffmann, and by Hare. Hall further discovered that if the feeding of a carnivorous animal with iron had been long continued, the metal could be detected in the pulp-cells of the spleen and in the hepatic acini around the central vein. The conclusion of Hall, that iron occurs in the human system in two forms, one a fixed organic combination,—hemoglobin,—the other an inorganic or a very loose organic combination, is very plausible. According to Hall, it is the second combination whose amount in the system continually varies with that of the iron taken into the alimentary canal.

**Physiological Action.\***—It has been generally taught that iron acts in anemia by supplying a missing element necessary for the nutrition of the body, that is, as a food. But, while it is probably true that in cases of iron starvation the salts of this metal may be utilized as a food by the system, it is much more likely that in anemic conditions iron acts as a direct stimulant to the blood-making organs.

To suppose that, because it is an essential constituent of hemoglobin, iron acts in the treatment of anemia as a food, is no more relevant than to claim that—because phosphorus is an essential constituent of the protoplasm, therefore, the administration of elementary phosphorus acts as a food; or to claim that—because strychnine is not a normal constituent of the protoplasm, therefore, it exercises no beneficial action upon the system. The fact that cases of chlorosis occur despite the daily ingestion of more than sufficient iron for the needs of the body, and that the administration of foods containing iron does not cure chlorosis, is very strong evidence that iron acts not as a food but as a direct stimulant influence upon the organs producing hemoglobin.†

Müller has found that in dogs rendered anemic by repeated bleeding and a diet as free as possible from iron the administration of an inorganic salt of iron increased the number of nucleated corpuscles in the blood. Moreover, Simon has shown that, not only is the hemoglobin increased by chlorosis, but also, that the blood globulins are augmented by iron.

The question whether or not iron acts as a stimulant to the blood-making organs is closely connected with the question as to the effect of iron upon healthy individuals. It was formerly believed that the

\* V. H. Meyers and F. Williams (*Arch. f. Exper. Path. u. Pharm.*, xiii, 76) have studied the effects of enormous doses of the iron and sodium tartrate upon the lower animals. Both frogs and mammals are killed by it, the symptoms in warm-blooded animals being vomiting, purging, great fall of the blood-pressure, muscular weakness, and finally coma and death. The experiments show that the heart is not much affected, but the vaso-motor system and the spinal motor centres are paralyzed.

† The theory of Kletziński, and of Bunge, that iron does good in chlorosis, by combining with hydrogen sulphide and thus preventing precipitation of food iron, has been shown to be false in both its pathology and its chemistry and has even been abandoned by Bunge himself.



proper administration of the metal to healthy man would produce an excess of the red blood-corpuscles, but more recent investigations, while somewhat discordant and not conclusive, have unsettled this belief.

The experiments of Nasse upon dogs are in favor of the older view, while those of E. C. Cutler and E. H. Bradford are in opposition to it. The first observer, giving iron with fat, noted that the specific gravity of the blood rose from 1052 to 1060.8, and the amount of the metal in the blood from 0.477 to 0.755 per thousand parts, both the result of increase in the corpuscular element. Cutler and Bradford experimented upon man, using the tubes of Malassez, the result being slight diminution of the red blood-disks. As, however, the experiments were only two in number, and the subjects not under complete control as to conditions of life, these observations can hardly be considered conclusive.

It appears to be a well-established fact that one of the functions of the red blood-corpuscles is to convert oxygen into ozone, which is the efficient form of the element in the system (see A. Sasse). The iron oxide outside of the body certainly possesses an ozonizing power similar to that of the red disk. Thus, a spot of iron mould—*i.e.*, iron oxide—on linen will in time destroy the fabric. The reason of this is the corroding action of the ozone which is slowly generated by the iron oxide. It would seem *a priori* probable that, by increasing oxidation an increase of the iron in the blood should cause elevation of temperature and increased elimination of urea. The studies of W. Pokrowsky have shown that, in cases of anemia, after the exhibition of iron the temperature does rise, even when in the beginning it was not below normal, and that simultaneously there is an increase in the daily elimination of urea; and the experiments of Botkin, as quoted by Sasse (we have not seen the original), establish the same fact in regard to healthy men. The increased oxidation cannot be due simply to an increase in the number of the red corpuscles, for while the latter accrue slowly, Pokrowsky found that the temperature sometimes rose within five hours after the exhibition of the first dose.

**Therapeutics.**—Leaving out of consideration those cases which may be spoken of as instances of “accidental anemia,”—*i.e.*, anemia due to hemorrhage, poison, starvation, or other temporary cause, which has passed off or is removable, and in which iron may be given as an aid to the rebuilding of the blood,—we find that practically the anemias are divided into two sets: those in which there is a pronounced lessening in the percentage of hemoglobin in the blood but not a corresponding lessening in the number of red blood-corpuscles, and those in which the red blood-corpuscles are greatly diminished in number. The first class of cases is typified in chlorosis, the second in pernicious anemia.

Of the value of iron in *chlorosis* there can be no doubt. Thus, Simon reports a case of chlorosis in which, under the steady use of iron for sixty-four days, the globulin increased from 30.86 parts to 90.80 parts per thousand, and the hemoglobin from 1.431 parts to 4.598 parts per thousand; and Cutler and Bradford have obtained confirmatory results with Malassez's tubes. In most cases of *essential anemia* with great lessening in the number of red blood-corpuscles, typified by *leukemia* and *pernicious anemia*, iron is of no service whatever. Unfortunately, the line between the two sets of cases of anemia is in nature not so sharp as it can be made in treatises, and we have seen cases presenting a chlorotic form of anemia, in which

the anemia failed to be affected at all by iron or any other treatment, remaining almost as persistent and unconquerable as the blood-lesion of leucocythemia.

Almost all the preparations of iron are more or less astringent, and when in the blood very probably exert a direct influence upon the tissues, contracting them not merely by increasing their tone, but also by acting on their vital contractility.

**Administration.**—When iron is used as a hematinic a preparation should be chosen which has little astringency. Among the most useful for administration in pill form are the mass of ferrous carbonate and the reduced iron, while, if a soluble preparation is desired, either the soluble phosphate or the iron and ammonium tartrate may be chosen.\*

Spurred on by the theory that the inorganic preparations of iron are not absorbed, pharmaceutical chemists have put forth many organic preparations. Of this multitude only one deserves any mention and that is the one commended by Schmiedeberg and Marfori, under the name of *ferratin*, a proteid compound containing from four to eight per cent. of iron, which is affirmed to be the form in which iron exists in the liver, and out of which in the body the hemoglobin is directly made. There is, however, neither clinical nor experimental evidence indicating that ferratin is superior to the older compounds. Hochhaus and Quincke found that ferratin and the older compounds could be traced through the duodenum into the mesenteric glands with equal facility; and in an elaborate study on the absorption and elimination of the iron, Cloetta was unable to perceive any difference between organic and inorganic preparations of iron in relation to their building up of the blood.

There are persons in whom iron produces headache: this can in some cases be obviated by the use of laxatives. The observations of M. Petit, N. A. Bubnow, etc., that the iron preparations in large doses inhibit the digestive processes, throw some light upon these cases. Our experience is that gouty or rheumatic patients bear iron badly, and that sometimes its exhibition seems to aggravate the arthritic symptoms. The chief contraindication for the use of iron is the existence of *plethora* or of catarrhal disease of the gastro-intestinal tract.

The peculiar actions of certain salts of iron will be considered under their respective preparations.

All of the salts of iron have chalybeate properties, although, in the case of some of the preparations, their other effects entirely outweigh their virtues as hematinics. The most notable of these preparations are as follows:

**SOLUTION OF FERRIC SUBSULPHATE**, Monsel's solution, is actively astringent and is used chiefly as a styptic for the control of local *hemorrhages*. It may also be used with advantage in the treatment of *hematemesis* in doses of from one to five minims, well diluted, given as often as necessary. In overdose Monsel's solution acts as an irritant poison. The chemical antidote should be an alkali in the form of soap or washing soda. *Sulphate of iron* is also astringent but is much more irritant and comparatively rarely employed.

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\* The alkaloidal compounds with iron are very ineligible preparations, because they do not allow the practitioner to vary the proportionate doses of the two ingredients.

TINCTURE OF CHLORIDE OF IRON, although widely used as a chalybeate, is, on account of its astringent properties, much more likely to produce gastro-intestinal disturbances than many other salts of iron. It, however, appears to possess certain peculiar properties which make it valuable. Decidedly diuretic and escaping through the kidneys, it directly affects the genito-urinary mucous membrane. It is much used in *chronic Bright's disease* and combined with tincture of cantharides in *gleet*. In *erysipelas* it is constantly employed with remarkable results, controlling the disease in a manner not yet understood. Analogy has suggested its employment in other adynamic affections, such as *diphtheria* and *pyemia*, but its value in these diseases is much more doubtful. It is so destructive to the teeth that except in the toothless its use as a gargle is unjustifiable; and even in its ordinary therapeutic use, by the employment of a tube, etc., the teeth should be protected as far as possible.

SYRUP OF FERROUS IODIDE combines the alterative effects of iodine with the tonic action of iron and is largely used in the treatment of *scrofula*. It has, however, no advantage and several disadvantages over the extemporaneous combination of an iodide with an iron salt.

FERRIC HYDROXIDE, also known as sesquioxide of iron and the hydrated oxide of iron, is used chiefly as an *antidote to arsenic*. It is formed when an alkali is added to a solution of an iron salt. In emergency any alkali and a soluble iron salt may be used to make the antidote, but *ferri hydroxidum cum magnesiæ oxido*, of the U. S. Pharmacopœia, which is made by adding an excess of magnesium oxide to a solution of ferric sulphate, has the advantages that the magnesia is non-irritant and is itself somewhat antidotal to arsenic. As the ferric hydrate is perfectly innocuous, and especially since it acts only when in excess, it should be very freely administered. A tumblerful of the ferric hydroxide with magnesia may be taken at once and repeated several times if necessary.

For antidotal purposes ferric hydroxide should be freshly prepared, and should be so moist as to constitute a magma. Its virtues are deteriorated by age, even when it is kept under water, and are entirely destroyed by drying. If the solution of the ferric sulphate be not at hand in an emergency, the chloride will yield just as useful a product, and sodium carbonate or, better still, magnesium carbonate, may be substituted, if circumstances necessitate it, for the ammonia. The precipitate falls at once, and may be washed by putting it in a piece of muslin, squeezing out the original fluid, and then pouring on some fresh water. Of the precipitated ferric hydroxide a tablespoonful may be given at a dose.

MANGANESE.—The salts of Manganese have been supposed to possess therapeutic properties similar to those of iron. The metal manganese certainly exists in the blood, but its salts have failed to gain the confidence of the profession, although highly recommended by Harmon, of Belgium, and by Pétrequin as an adjuvant to the chalybeates. In Garrod's experiments upon anemia the preparations



of manganese failed to be of service. According to C. C. Gmelin, the sulphate acts as a powerful cholagogue on the lower animals, and Thomson states that it is a purgative to man in doses of one or two drachms. Leand affirms that the manganese oxide is therapeutically equivalent to the preparations of bismuth excepting in that it does not constipate, and that it may be used with advantage in *gastralgia*, *pyrosis*, and similar stomachic derangements.

#### Official Preparations:

Mangani Dioxidum Præcipitatum.....	5 to 10 grains (0.3-0.6 Gm.).
Mangani Hypophosphis.....	5 to 10 grains (0.3-0.6 Gm.).
Mangani Sulphas.....	5 to 10 grains (0.3-0.6 Gm.).

### MINERAL ACIDS.

Sulphuric, hydrochloric, nitric, and nitrohydrochloric acids, when in concentrated form, rapidly destroy all organic tissues, and are, therefore, corrosives, hydrochloric acid being the feeblest.

Owing to its abstraction of the element of water from the carbon of organic tissues, sulphuric acid blackens organic matter at the same time that it destroys its texture; nitric acid stains organic tissue a deep yellow color; nitrohydrochloric acid produces a somewhat similar but much less pronounced discoloration. In the detection of poisoning by one of these agents the color of the stain upon the person or clothing is often of great assistance. Holes made in the linen by one of these acids are to be distinguished from those made by fire or mechanical violence by the pulpy character and acid reaction of the edges.

The general symptoms of poisoning by mineral acids are similar, and depend for their severity especially upon the amount and the concentration of the dose taken, although sulphuric and nitric acids are more powerful than is hydrochloric acid.\* Death from collapse has resulted in two and a half hours, but months may be required in the working out of the fatal result. The symptoms are immediate pain in the mouth, gullet, and epigastrium, violent vomiting (after sulphuric acid the matters may be tarry), and rapid collapse marked by cold wet surface, feeble pulse, and suppressed voice. The mind is usually clear until very late in the poisoning.

After a small dose the chief symptoms may be connected with the upper digestive passages. Thus, Maukopff has recorded suppurative parotitis largely due to the closure of the duct of Steno. Ulceration of the larynx or œsophagus has frequently been noted. Desquamative nephritis may be developed several days after subsidence of the first symptoms. In a case of sulphuric-acid-poisoning recorded by Maukopff, the urine which had ceased to be albuminous on the third day became so again on the twentieth, with a simultaneous development of casts containing blood-corpuscles; after

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\* Cases of sulphuric-acid-poisoning (*Med. Times and Gaz.*, 1863, i.).

death tubular nephritis was found. Another symptom noted by Maukopff was intercostal neuralgia.

After death, destruction of the œsophagus, stomach, or air-passages is usually found, the color of the slough—black after sulphuric, yellow after nitric acid—being characteristic. Probably in all cases in which death does not take place too early, wide-spread degeneration of protoplasm takes place. A. D. Kazowsky has found that this involves the cells of the heart-ganglia, which undergo parenchymatous swelling, followed by necrosis of the cells and vacuolization not only of the nuclei but also of the general protoplasm.

When the dose has not been sufficient to kill, protracted illness from local organic alterations usually results.

The treatment of a case of acid-poisoning consists in the immediate administration of soap, chalk, whitewash, magnesia, or other available antidote. Notwithstanding Christison's condemnation of the alkaline carbonates as too irritating, they should be used unhesitatingly in dilute form if immediately at hand.

**SULPHURIC ACID.**—*Oil of Vitriol* is, when pure, a colorless, heavy liquid which on exposure to the air rapidly absorbs moisture. The official acid has a sp. gr. of 1.826.

#### Official Preparations :

Acidum Sulphuricum.....	Not used internally.
Acidum Sulphuricum Dilutum (10 per cent.).	15 to 30 minims (1-2 C.c.).
Acidum Sulphuricum Aromaticum (20 per cent.).....	15 to 30 minims (1-2 C.c.).

Concentrated sulphuric acid is not rarely used as an escharotic, for which purpose it is mixed with finely powdered charcoal so as to form a paste. Appropriately diluted, it has been employed as a stimulant and astringent lotion in *venereal* and other indolent *ulcers*. Internally, sulphuric acid is very useful as an astringent in *colliquative sweats* (*night-sweats*) and in profuse *serous diarrhæas*. We have used it with great advantage in the sudden serous vomiting and purging of infants known as *cholera infantum*.

It has been employed with advantage in *cholera*, and a remarkable series of observations by R. G. Curtin at least furnish good reason for further testing its powers as a prophylactic against this disease.\*

The facts recorded by Curtin are as follows. A very severe epidemic of the disease ceased in the Insane Department of the Philadelphia Almshouse within twelve hours after the lunatics were all put upon the free use of sulphuric acid lemonade, the only new case after this being in a man who refused to use the prophylactic. Two days after the use of the sulphuric acid was stopped two new cases occurred, and the epidemic was again arrested by the use of the acid. In the surgical wards of the Hospital Department the acid was used from the beginning of the epidemic; and these wards, although in no way isolated, were the only parts of the institution unvisited by the disease. The sulphuric acid probably acted by

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\* It is very probable that other acids are equally antidotal to the cholera germ, since Richard P. Strong found that the addition of one per cent. of *citric acid* to water infected with the cholera germ made it safe to drink.—*Report Government Laboratories, Philippine Islands*, Sept. 1, 1903.

producing an excessive acidity of the alimentary canal, it being well assured that the cholera organism will develop only in an alkaline condition of the alimentary tract. Thus, the dog, whose digestive tract is highly acid, resists the action of the bacillus unless an alkaline carbonate be freely given, when choleraic symptoms appear after the administration of the cholera organism.

Sulphuric acid was formerly used in *hemorrhages*, but is now rarely employed. It is, we think, much less efficacious than are some other remedies. In *acute lead-poisoning* the dilute acid is an efficient antidote, and in white lead works the free use of sulphuric acid lemonade by the employees is said to be advantageous as a prophylactic against the chronic poisoning.

**Administration.**—Sulphuric acid should be given properly diluted, and with the requisite precautions to prevent its injuring the teeth.

**HYDROCHLORIC ACID** is a colorless aqueous solution of hydrochloric acid gas, having the specific gravity of 1.158 and containing 31.9 per cent., by weight, of the gas. The yellowish tint of commercial hydrochloric acid is due to the presence of ferric chloride, or organic matter.

#### Official Preparations:

Acidum Hydrochloricum (32 per cent.).....Not used internally.  
Acidum Hydrochloricum Dilutum (10 per  
cent.).....15 to 60 minims (1–4 C.c.).

Hydrochloric acid, being the normal digestive acid of the stomach, is often advantageous in cases in which chronic *indigestion* is connected with the failure to secrete acid in the stomach, and the combination of it with strychnine, bitter tonics, and aromatics is often serviceable. In the so-called “Swedish plan” of treatment of *typhoid fever*, hydrochloric or other mineral acid is given in very large quantities. Although the method was at one time much in vogue, it has no justification in results, and is to be avoided. The local use of hydrochloric acid in *diphtheria*, made famous by Bretonneau, has deservedly gone into oblivion. As a poison, hydrochloric acid is the most feeble of its class, recovery having occurred after the ingestion of an ounce.

**NITRIC ACID** is a liquid of the specific gravity of about 1.403, which as first made is colorless, but by exposure to the light acquires a yellow tint. It oxidizes all the common metals except gold, and is exceedingly corrosive to living tissue, which it stains an indelible yellow. When diluted it converts most animal and vegetable substances into oxalic, malic, or carbonic acid.

#### Official Preparations:

Acidum Nitricum (68 per cent.).....Not used internally.  
Acidum Nitricum Dilutum (10 per cent.).....15 to 60 minims (1–4 C.c.).



When taken internally in small amount, nitric acid acts as a stimulant upon the glandular system of the alimentary canal, and in *serous diarrhæa* appears to exert an astringent influence.

Nitric acid is frequently used as a powerful escharotic in cases of *chancre*, *venereal* or other *warts*, *hospital* and other *acute gangrenes*. In many instances in which formerly it was relied upon it has been replaced by antiseptic measures.

In its employment care should be taken to protect the sound tissue by oil or, still better, by a layer of soap. It may be applied by means of a splinter of wood, or, if it is to be used more freely, by a little mop. When it has penetrated as deeply as is desirable, washing the part with warm soapsuds will prevent further action.

Internally, nitric acid has been used in *low fevers*, but with very doubtful advantage. In *dyspepsia*, in *chronic hepatic congestion*, in the *oxalic acid diathesis*, and in the *dyscrasia of constitutional syphilis* nitric acid has been employed with advantage, but is much inferior to nitrohydrochloric acid.

In 1826 Hope asserted that NITROUS ACID has a specific action in *serous diarrhæa*, including the sudden acute diarrhœas of hot climates, and in the chronic *dysenteries* originating under similar circumstances. The formula he employed is as follows: R Acidi nitrosi, fʒi; Misturæ camphoræ, fʒviii; Misce, et adde Tinct. opii, gtt. xl. S.—A fourth part to be taken every three or four hours.

Under the name of *Hope's Camphor Mixture* a preparation similar to this has been much used (*Mistura Camphoræ Acida*, N. F.) but has gradually lost the confidence of the profession, chiefly, we believe, because on theoretical grounds the original formula has been departed from. The Nitrous Acid of the shops is an orange-red liquid, which may be looked upon as a solution of nitric oxide in nitric acid. When it is diluted with water it is after a short time converted into simple nitric acid. For this reason it has been customary to substitute nitric acid for the Nitrous Acid of Hope's original formula. It should be noted, however, that the latter provided only sufficient of the remedy to last a few hours, and, as the reaction which has been spoken of requires some time for its performance, we do not think that theory in truth warrants the change. Practically we have failed with the new formula, when immediate relief was afterwards obtained by the use of the medicine prepared according to the old plan. Made in this way and used while fresh, Hope's Camphor Mixture is a very efficient though disagreeable remedy in *serous diarrhœas* connected with disordered secretion of the liver and other glands of the alimentary canal.

NITROHYDROCHLORIC ACID is made by mixing nine parts of nitric acid with forty-one parts of hydrochloric acid. If the acid be sufficiently strong, an orange-colored liquid will be formed with the evolution of intensely irritating vapors.

After standing for a length of time, the *red* color of freshly mixed nitrohydrochloric acid changes to a golden yellow. It is in this state that the U. S. Pharmacopœia directs the acid to be used. By longer standing the *golden* yellow becomes *lemon* yellow, and the odor of chlorine is almost entirely lost. These changes are hastened by light, but will occur in the dark and in well-stopped bottles. Although the golden-yellow acid is directed by the Pharmacopœia, yet careful clinical studies have convinced us that the acid acts much more efficiently when freshly prepared

and of a deep red color. In some cases it has seemed to us useful only when in the latter form. The lemon-yellow acid is comparatively inactive.

#### Official Preparations :

Acidum Nitrohydrochloricum, . . . . .	3 to 8 minims (0.2-0.5 C.c.).
Acidum Nitrohydrochloricum Dilutum, . . . . .	15 to 30 minims (1-2 C.c.).

The remedial value of nitrohydrochloric acid depends chiefly upon the power which it possesses to a much greater degree than any other of the mineral acids of influencing the action of the liver and other glandular organs of the alimentary canal. Originally proposed by Scott, of Bombay, in the *chronic hepatitis* of hot climates, it has been used with great success by Annesley, Martin, and other famous India surgeons. The remedy would seem not to be indicated in hepatitis with high fever and a tendency to rapid suppuration so much as in the slower form of the affection, which normally ends in chronic enlargement and induration of the viscus. Both in the habitual *congestion* of the *liver* and in the milder affection known as *biliousness*, whose pathology is probably a torpid condition of the small glands of the alimentary mucous membrane as well as of the liver, nitrohydrochloric acid has yielded in our hands most excellent results. That the remedy does act upon the liver is proved by the fact that in these cases it sometimes produces violent bilious diarrhœa. When *jaundice* depends upon obstruction or upon any of the severer organic diseases of the liver, the acid is of little if any use; when, however, the jaundice depends upon torpor of the liver, or even when it is catarrhal in origin, the remedy may be of great service. Even in the early stages of *cirrhosis*, while the liver is still enlarged, nitrohydrochloric acid should be tried, as in some cases apparently of this character great benefit has been derived from its use.

In those forms of *chronic diarrhœa* in which the disease is really an intestinal dyspepsia, nitrohydrochloric acid may be of great service. As the effect of the acid is not a sudden one, it is evident that it acts in these cases not as an astringent, but by restoring the normal digestive power.

There is a morbid condition, *oxaluria*, probably dependent upon defective primary assimilation, in which the chief symptoms are general malaise, a feeling of weakness, a lack of elasticity, and a very great depression of spirits, with the crystals of calcium oxalate generally present in the urine, and in which nitrohydrochloric acid produces in a few days a surprising revolution.

As a "blood-purifier" the acid has been employed in *constitutional syphilis* and in various ulcerative *skin affections*. In these diseases it no doubt does good by improving digestion and increasing glandular action, but there is no reason to believe that it is a direct alterative.

**Administration.**—For reasons which have already been given, when nitrohydrochloric acid is administered internally it should be freshly prepared; and, as the changes which have been spoken of take place more rapidly when the acid is mixed with water, the

*diluted* nitrohydrochloric acid is an ineligible preparation. As light hastens its deterioration, the acid should always be kept in a dark bottle with a glass stopper. Directly after mixing the acids the evolution of gas may be so great as to necessitate its being allowed to escape. After six or eight hours, however, the bottle should be closely stopped. The acid should be properly diluted, and taken through a tube after meals.

In *chronic hepatic diseases* the external application of the acid appears to give even better results than its internal use. In India, according to Sir Ronald Martin, the bath is used as follows:

Take Hydrochloric acid f ʒ iii, Nitric acid f ʒ ii, Water f ʒ v. Mix. Two gallons of water and six fluidounces of the above mixture suffice for a bath, which will keep fit for use during three days, provided half a fluidounce of acid and a pint of water are added morning and evening. The bath must of course be given in wooden or earthenware vessels, and if it becomes necessary to warm it only a portion should be heated and the rest then added. In urgent cases the whole body may be immersed in the bath; but generally a foot-bath is preferable, the inside of the thighs and arms and the hepatic region being at the same time sponged. The bath should be repeated twice daily, lasting each time for ten or fifteen minutes.

We have had no experience in this method of using nitrohydrochloric acid, but have derived great benefit from the application of the acid over the hepatic region.

A large piece (eight by ten inches) of spongio-piline, or of canton flannel (several layers), should be wrung out in a lotion of a strength varying, according to the irritability of the patient's skin, from one to three fluidrachms to the pint, and applied over the right hypochondrium, and covered with a piece of oiled silk supported by a bandage. The application sometimes causes a prickling sensation, and after a time may produce a profuse local sweating. The dressing may be left on from half an hour to an hour, and be repeated three or four times a day: some patients can wear it almost continuously.

**PHOSPHORIC ACID**—Orthophosphoric acid ( $H_3PO_4$ ) results from the burning of phosphorus in the air, but is prepared commercially by the action of sulphuric acid upon bone-ash, which consists chiefly of calcium phosphate. The official acid contains eighty-five per cent. of the tribasic acid of chemists.\* It is a colorless, inodorous, sour liquid, of a syrupy consistence, which has a very acid reaction, and is corrosive to animal tissues.

**Therapeutics.**—Phosphoric acid has been used considerably as a tonic and alterative, especially in scrofulous diseases, but seems to have no other value than that of a very feeble and doubtful stimulant to the digestive apparatus

#### Official Preparations:

Acidum Phosphoricum.....	5 to 10 minims (0.3–0.6 Gm.).
Acidum Phosphoricum Dilutum (10 per cent.).....	$\frac{1}{2}$ to 1 fluidrachm (2–4 C.c.).
Sodii Phosphas †.....	30 grains (2 Gm.).
Calcii Phosphas Præcipitatus.....	15 grains (1 Gm.).

\* It has been affirmed that the *bibasic pyrophosphoric acid* is a cardiac sedative (see *Journ. of Anat. and Physiol.*, xi.).

† For description of sodium phosphate as a cathartic see p. 503.



**CALCIUM PHOSPHATE.**—*Precipitated Calcium Phosphate* is a white, inodorous, tasteless powder, almost insoluble in water or alcohol but soluble in dilute acids. Calcium phosphate is an abundant ingredient of bone, but also exists in notable quantities in all the tissues, and is probably as essential to their health as to that of bone. Whenever it is taken out of the food of animals, although they be otherwise well fed, sooner or later they waste, sicken, and die.

Chossat fed pigeons exclusively on corn containing very little of the calcium phosphate, and found that after some months they wasted, were affected with diarrhœa, and died. According to Roloff, a herd of cows which had been fed upon hay from a certain meadow were very much out of health, and suffered from *fragilitas ossium*. On examination, the hay was found to be nearly free from earthy salts, and upon bone-meal being given to the cows they recovered their health in four weeks. The same authority further states that in some meadows with which he is acquainted the disease is endemic among the cows because the grass is so poor in phosphates. Haubner also affirms that cattle fed exclusively upon potatoes, or upon roots very poor in phosphates, fail to fatten, become weak, and are likely to suffer from caries, but that if the calcium phosphate be given they rapidly improve; and E. Voit states that rachitis without emaciation can be produced in three or four weeks in young dogs by taking the calcium phosphate out of the food.

Hegar has considered the absorption of the calcium phosphate, when given as a medicine, very doubtful, because when he exhibited it freely there was no increase in the amount of the phosphoric acid or of the earthy bases in the urine. Böker, on the other hand, has found that if the drug be given to those wet-nurses whose milk contains an abnormally small amount of phosphates, the milk soon becomes rich in the earthy salts, and L. Perl has found that administration of the phosphates is followed by an increase in their amount in the urine. Further, Albert Riesell has shown that the phosphates are eliminated by the intestines, and therefore that even if it were a fact that their renal excretion is not augmented by their administration, it would not prove that they are not absorbed. Teissier has found that in the early stages of phthisis there is a very great increase in the excretion of the earthy phosphates by the kidney, and the researches of Beneke\* are said to have shown that this increased renal elimination, which plainly occurs in several allied diseases, is not accompanied by any increase in the amount ingested in the food or decrease of the amount eliminated by the intestines, and that, consequently, there is a very decided wasting of the normal phosphates of the body. This being so, the use of phosphates in these diseases is as rational as that of iron in anemia.

**Therapeutics.**—According to Dusart, to Beneke, and to Teissier, the diseases in which the calcium phosphate is especially indicated are *rachitis*, *osteomalacia*, *phthisis*, and *scrofulosis*. It is evident that the indications for the earthy salts are very strong in the first two of these affections, and clinical experience has certainly

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\* We have not had access to the original memoir of Beneke (*Zur Würdigung des Phosphors. Kalkes in physiolog. und therapeut. Beziehung*, Marburg, 1870). See *Schmidt's Jahrb.*, cli, 138.

borne out the results of *a priori* reasoning. In *scrofulosis* the call for the drug is not so plain; but Beneke states that in many cases, if the urine be examined, it will be found to be abnormally rich in earthy phosphates, and that under these circumstances the remedy is of the greatest value. Cases are not rare of children of slow development, often seemingly well nourished and robust, and yet really pale and with flabby flesh, but without any distinct symptoms or marks of scrofulosis or of rachitis. Under these circumstances, the child is in a condition allied to that of the diathesis spoken of, and calcium phosphate is serviceable. In cases of *delayed union* after *fracture* the present remedy is seemingly indicated, especially since Dusart has experimentally proved that when given to animals whose bones have been broken it hastens union and makes the callus abnormally heavy and firm. Calcium phosphate has been recommended in various diseases other than those mentioned, but its value in them is much more doubtful. Bennett commends it in *chronic phthisis*; Piorry, in *syphilitic periostitis*; Beneke, in *syphilitic gummata*; Schönnian, and also Kugelman, in the *menorrhagia* of anemic women. Beneke calls attention to the use of it during *pregnancy*, and believes that it exerts an influence on the foetus, so that women who have borne only rachitic children will bring forth healthy offspring.

**Administration.**—Calcium phosphate is usually administered dissolved by means of lactic acid in conjunction with cod-liver oil, especially as the so-called emulsion of cod-liver oil and *lactophosphate of lime*, which, when properly prepared, contains fifty per cent. of cod-liver oil and two grains of the calcium phosphate to the drachm. Dose, one to four teaspoonfuls.

HYPOPHOSPHOROUS ACID is never used internally in a pure condition, but various combinations of it with mineral bases and alkalis have been largely used as tonics and reconstructives in the debility of *phthisis*, *neurasthenia*, and allied conditions. In our experience these combinations have seemed to exert no other influence in disease than that of their active bases. According to the researches of Paquelin and Joly and of A. Boddart, the hypophosphites are rapidly eliminated through the kidneys in an unchanged condition. Boddart affirms, on what we believe to be insufficient evidence, that they increase distinctly the elimination of urea, of phosphorus, and of chlorine.

#### Official Preparations:

Acidum Hypophosphorosum (30 per cent.)	... Not used internally.
Acidum Hypophosphorosum Dilutum (10 per cent.)	..... 8 to 15 minims (0.5–1 C.c.).
Calcii Hypophosphis	..... 15 grains (1 Gm.).
Ferri Hypophosphis	..... 8 grains (0.5 Gm.).
Potassii Hypophosphis	..... 15 grains (1 Gm.).
Sodii Hypophosphis	..... 15 grains (1 Gm.).
Syrupus Hypophosphitum	..... 1 to 2 fluidrachms (4–8 C.c.).
Syrupus Hypophosphitum Compositus	..... 1 to 2 fluidrachms (4–8 C.c.).

GLYCERO-PHOSPHORIC ACID.—As is well known, the nervous tissues of the body contain a notable percentage of phosphorus. It is present in the form of glycerophosphoric acid. This fact has led to its employment as a nerve tonic in such conditions as *neurasthenia*, *locomotor ataxia*, and *phosphaturia*, with results asserted to exceed those obtained from phosphorus in any other form. It is given either in the form of the acid itself or of sodium or calcium glycerophosphate in doses of two to five grains (0.1–0.3 Gm.).

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## MINERAL ACIDS.

- CURTIN.....P. M. T., iii, 649.  
 KAZOWSKY.....Centralb. f. Allg. Path. u.  
 Path. Anat., 1894, v.  
 PREYER.....C. M. W., 1875, 578.



### FAMILY III.—ALTERATIVES.

THERE are employed by practitioners of medicine, to affect certain diseases most intimately connected with the processes of nutrition, various substances which do not, at least in the doses commonly used, produce any very obvious symptoms. It is to medicines of this character that the name of *Alteratives* has been applied, because when administered they seem simply to alter morbid processes.

Speculation has been rife as to the mode in which alteratives influence the body; and as the accepted pathology has been humoralistic or otherwise, so has it been strenuously argued that they act upon the vital fluid, or upon the solids of the body. The term "purifying of the blood" has been especially applied to their action, and is sufficiently suggestive of their function as viewed from the pathological stand-point of the old humoralist. What we know of the action of these medicines at present amounts to this, that they modify the nutritive processes of the body. To deny, as has been done, the existence or value of medicines of this class because we cannot tell why mercury relieves syphilis or why potassium iodide cures rheumatism is as absurd as to deny the existence of the syphilitic and the rheumatic dyscrasia because we do not know their ultimate nature.

#### PHOSPHORUS.

Phosphorus is a translucent, when pure nearly colorless, but usually slightly yellowish, highly inflammable elementary body, which is tasteless, but possessed of a peculiar alliaceous odor. It is insoluble in water, sparingly soluble in ether, absolute alcohol, and the oils, freely so in chloroform. It takes fire at 100° F., and melts at 111.2° F. In the shops it is in cylindrical sticks, covered with a whitish layer, and having, when cut, a waxy consistence and lustre. It occurs in several allotropic forms,—red phosphorus, black phosphorus, and the crystallized metallic phosphorus of Hittorf, whose physiological properties have not been investigated.

#### Official Preparations :

Phosphorus.....	$\frac{1}{100}$ grain (0.6 Milligm.).
Pilulæ Phosphori.....	Each $\frac{1}{100}$ grain (0.6 Milligm.). 1 pill.

*Absorption and Elimination.*—It has been demonstrated that phosphorus passes into the blood as phosphorus, and not in the form of phosphoric acid or other compound.

In cases of poisoning in men the breath is said to be sometimes distinctly phosphorescent, and in animals Bamberger has found phosphorus in the blood, and Husemann and Marmé in the liver two or three hours after its ingestion. W. Dybrowsky has detected it in the blood and liver ten hours after its ingestion, and other observers have demonstrated its presence in almost all of the tissues. It seems probable that to some extent it finds entrance into the circulation by being

dissolved in the various fatty matters contained in the alimentary canal. At the temperature of the body, however, it yields abundant vapors, and Bamberger has demonstrated that these readily and rapidly pass through animal membranes. He has found that defibrinated blood, when separated from the fumes of phosphorus only by an animal membrane, rapidly becomes saturated with the poison. Dybkowsky has confirmed this, and it cannot be doubted that in a similar manner living blood absorbs the poison from the alimentary canal. W. Dybkowsky's research renders probable the theory of Schuchardt that the phosphorus is converted to some extent in the alimentary canal, but much more largely in the veins, into phosphuretted hydrogen, and that some of this compound and some of the phosphorus itself is oxidized in the venous blood, so that phosphoric acid, besides phosphorus and phosphuretted hydrogen, is emptied into the arterial blood; further, that the last two compounds are oxidized at the expense of the arterial blood and the tissues it feeds, and that the poisoning is due to this deprivation of oxygen. For the details of the experiments upon which these conclusions rest we must refer the reader to the original memoir.\* According to Plaiice, phosphorus is not found in free condition in these cases in the urine.

**Physiological Action.**—The physiological action of phosphorus in therapeutic doses is probably entirely different from that which it exerts when in larger amounts. It is a constituent of most of the more important tissues, and is especially abundant in the nerve-centres, upon whose nutrition it is believed by many to act as a stimulant. So far as the nervous system is concerned, this assertion rests upon clinical observation; but Wegner (confirmed by S. Miura and W. Stoeltzner) has experimentally demonstrated such an action upon the bony tissues. When adult animals are fed upon minute doses of phosphorus the spongy tissue in the long and short bones becomes thickened and the compact tissue more dense. After a time new tissue is deposited upon the inside of the shafts of the long bones, in some instances until the marrow cavity is obliterated. The action upon the bones of growing animals is even more marked.

For reasons already adduced (see page 338), it is certain that in poisonous doses phosphorus enters the blood in its elemental form. Wegner advances the following reasons for believing that therapeutic doses act as phosphorus upon the bony tissues. First, no similar action can be obtained from phosphoric acid unless from eight hundred to one thousand times the proportional dose be given. Second, the newly formed tissue is at first gelatinous. Third, there is no excess of phosphates in the bone. Fourth, when the food is deprived of lime the same new tissue arises, but remains in a soft, gelatinous state.

**Therapeutics.**—Phosphorus was at one time believed to be a diffusible stimulant, and it possibly may exert such an influence. In the acute nervous exhaustion of *typhoid pneumonia* we have once or twice seen it apparently act favorably in this way. The chief use of phosphorus in medicine is as a nutrient tonic to the nervous system. In all cases of chronic *nervous exhaustion*, whether involving

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\* M. Lecorché (*Archives de Physiologie Normale et Pathologique*, 1868, i., 1869, ii.) believes that phosphorus acts in the blood as phosphoric acid, but does not establish his opinion. For a discussion of this, see Dybkowsky's paper.

the cerebral or the spinal centres, it is of great value; even when the symptoms strongly suggest organic disease, as in threatening *cerebral softening* or *myelitic paraplegia* from excessive venery, it is often of service. It has been strongly extolled in *neuralgia* due to nervous exhaustion.

It is probable that it may be of value in some cases of impaired vitality although the nervous system be not obviously implicated. H. Eames states that he has obtained great benefit from its use in obstinate skin affections, such as *lupus*, *acne*, and *psoriasis*. S. R. Percy has used it successfully for repeated *furuncular* eruptions. It has also been asserted to be useful in *cataract*.\*

On account of its marked influence on the development of bone, Wegner suggested its use in *osteomalacia* and in *rickets*, and thereby started a large amount of clinical experimentation and a considerable clinical literature, in which there is some contradiction: the general result, however, has been to establish the value of the drug in rachitic cases, especially in those in which there is a tendency to *osteoporosis*. As large doses as can be borne without derangement of the digestion should be given.

**Toxicology.**—The ingestion of a fatal dose of phosphorus is not followed by any sensible effects for some time. After, however, from three to twelve hours a sense of weakness and of general wretchedness manifests itself, usually accompanied, or soon followed, by nausea and vomiting, and in most cases the patient soon complains of abdominal pain, the severity of which, however, never equals that of corrosive poisoning. The matters vomited consist of food, mucus, and bile. During the first eight or ten hours they often smell strongly of phosphorus, and are luminous in the dark. The vomiting may persist during the whole attack, but generally there is an almost complete remission of symptoms on the second or third day.

The tongue is whitish or abnormally red, sometimes furred. There are generally fever (Maukopff), loss of appetite, and thirst. Later in the poisoning there is very often a remarkable fall in the temperature, which is generally, but not always, a precursor of death. The lowest point we have seen noted was 31.2° C. (88.2° F.) some hours before death.† In some cases fever is altogether absent, or comes on just before death.‡

The stools are at times normal in character and frequency, but there is general diarrhoea or constipation, with flatulence. Late in the attack the passages are in most cases very light clay-colored, or even whitish, and exceptionally they are bloody. In some cases they are phosphorescent.

Jaundice comes on in from thirty-six hours (Maukopff and Tüngel) to five days (Lebert and Wyss) after the ingestion of the poison. In most cases it appears first in the conjunctiva, but sometimes the

\* Tavnigot (*Revue de Thérapeutique Médico-Chirurgicale*, August and September, 1871) and Gioppi (*Giornale d'Oftalmologia*, abstract in *N. Y. Medical Record*, 1872).

† Battmann (*Archiv der Heilkunde*, 1871, 257).

‡ Concato (*Sydenham Soc. Year-Book*, 1869-70, 454).



urine gives previous warning of its approach. In some cases there is with it a decided and palpable increase in the size of the liver, which may pass, if the patient live long enough, into an equally apparent lessening of the bulk of that viscus. There is frequently pain and tenderness over the region of the liver. The severe nervous symptoms are rarely, if ever, developed until after the jaundice, although early in the attack there are not infrequently anxiety, headache, giddiness, and dreamy unquiet sleep, or even sleeplessness. The more pronounced nervous symptoms consist of delirium, which may be wild and is very frequently erotic, with somnolence ending in coma and death, occasionally preceded by convulsions. According to Taylor, the latter are a certain sign of approaching dissolution. Very generally partial spasms and fibrillary contractions of the voluntary muscles occur, although there is always, in not too rapid cases, progressive paresis of the voluntary muscles. Death is usually put off beyond twenty-four hours, yet it has occurred in a child in four hours and in an adult in seven hours; also in nine hours. The patient may suddenly succumb to collapse and cardiac paralysis, but more commonly dies comatose from a gradual failure of respiration and circulation.

If recovery occur it is by a gradual amelioration of the symptoms, and the health of the patient is apt to be impaired for some time, the most marked disturbances usually being the digestive and nervous symptoms. Apparently desperate cases will sometimes convalesce unexpectedly, and Tümgel states that a favorable issue may take place even after violent delirium.

The urine is almost always much affected by the poison. Very commonly it is scanty or albuminous, and sometimes it contains sugar.\* As was first pointed out by Munk and Leyden, after jaundice has set in, bile-acids, as well as biliary coloring-matter, are always to be found in the urine. Not infrequently a cloudy sediment consisting in part of epithelial cells, often tinged with bile, is deposited. Oswald Kohts and other observers have found leucin and tyrosin in the urine of dogs poisoned with phosphorus, and undoubtedly these substances may occur. Wohlgemuth has found besides these bodies arginin in the urine of a rabbit poisoned with phosphorus. The albuminuria generally follows, but may precede the icterus. A very remarkable and apparently constant constituent of the urine is sarcolactic acid. Fat has been found in the urine inside of renal epithelial cells, and also as free globules (Schultz).

In some instances phosphorus-poisoning presents symptoms quite different from the typical array. Death may take place in a few hours, and in such cases jaundice is not generally present. Zeidler reports a death in forty-two hours, from suppression of urine, with collapse and erotic delirium. In a case of Bollinger's the chief symptoms were vomiting, pain and tenderness over the abdomen, great

\* In only six of one hundred and forty-one consecutive cases of phosphorus-poisoning in the Medical Clinic of Prague was sugar found in the urine (*Zeitschr. f. Heilkde. N. F.*, ii. 8 u. 9, p. 339, 1901). As originally stated by Von Jakseh, the sugar is probably of secondary origin, due to the alterations of the liver.

weakness of pulse, gradually developed paralysis of the legs, and death, without jaundice, in four and a half days. The autopsy revealed hemorrhagic effusion between the membranes and the spinal cord, and also into the sheaths of the proximal portions of the spinal nerves.

In women, fatal doses of phosphorus very commonly produce a bloody pseudo-menstrual discharge, or, when pregnancy exists, abortion. M. Miura has found in the fetus of poisoned rabbits structural changes similar to those of the mother.

*Sub-acute phosphorus-poisoning* is said sometimes to be manifested by symmetrical gangrene of the extremities. (See W. K. W., 1901, No. 52.)

*Post-Mortem Appearances.*—The most characteristic lesions found after death from phosphorus-poisoning are wide-spread fatty degenerations involving practically all of the organs, but especially marked in the gastro-intestinal mucous membrane, the liver, and the kidney; an inflammation of the glands around the pylorus; and hemorrhagic extravasations.

As was first pointed out by Virchow, there is universally a gastro-adenitis, which causes the gastric mucous membrane to become thickened, opaque, whitish, grayish, or yellowish-white. This gastro-adenitis is not due to a local action of the phosphorus, because it occurs when the poison is introduced through other channels than the mouth. The duodenum and intestines suffer similar changes.

The liver is generally very much enlarged, friable, and light-colored; sometimes it is mottled, and sometimes portions of it are deeply stained with bile.\* The cells are gorged with fat-globules,† and in some cases there are small-celled interstitial thickenings due to hyperplasia of the trabecular tissue. The gall-bladder may be full or empty. In protracted cases the liver undergoes atrophy, with destruction of its secreting cells. According to the researches of Arthur Heffter, the percentage of lecithin in the liver, which is fixed in health, is greatly lessened in phosphorus-poisoning. The kidneys, especially in their cortical portion, suffer a degeneration similar to that of the liver, the epithelium becoming enlarged, granular, fatty, and finally undergoing destruction. The voluntary and cardiac muscles, the spleen, the lungs, and probably all the tissue, partake of the universal fatty degeneration‡ which Wegner has shown to involve even the minute arterioles.

The nervous system does not escape. As long ago as 1880 Danillo declared that he had found a myelitis in phosphorus-poisoning, and Gurrieri has discovered in the poisoned dog degenerations of various portions of the spinal cord; while it has been shown by Uziemblo that profound alterations take place in the retina, which becomes oedematous, with marked alterations in the vessels, hemorrhagic extravasations, and necrotic degeneration of the nervous cells.

The blood is often profoundly affected (Taussig and Corin and Ansiaux), becoming very dark, more or less completely losing its power of coagulation, and apparently suffering also in its corpuscular elements; echymoses are almost uni-

\* According to researches made by Emile Rousseau in the Pathological Laboratory of the University of Pennsylvania, the first anatomical changes in the liver occur in the centre of the lobules around the hepatic vein.

† A. Lebedeff (*Arch. f. Physiol.*, 1883, xxxi. 11) believes that the fat in the liver is not produced by degeneration of the hepatic tissue, but has simply been transported there from the subdermal regions. He bases this opinion upon his own observations,—first, that the phosphorus fat has the same chemical constitution as has subdermal fat; second, in a dog which had been fed with linseed oil and then poisoned with phosphorus, the liver was loaded with linseed oil. This evidence is of very little value, because on the one hand the linseed oil probably accumulated in the dog's liver before the poisoning and simply remained over, and on the other hand there is no proof that fat produced by degenerative changes necessarily differs in composition from other fat. The fact that the liver and other organs are destroyed in phosphorus-poisoning may be considered proof that the fat is formed out of the affected tissue; although this seems contrary to the allegation of Bergeat (*Gesellsch. f. Morph. u. Physiol. München.*, 1888), that in very emaciated animals the phosphorus-poisoning may run its course without the formation of fat.

‡ For full discussion of the pathology of phosphorus-poisoning, see Ziegler (*Beiträge Path. Anat.*, ii.), G. Kronig (*Virchow's Archiv*, 1887, ex.), Aufrecht (*Deutsch. Arch. Klin. Med.*, 1897, lviii.), Hans Schmaus, (*Münchener Med. Wochens.*, 1897, xlv, also 1898, xlv.), Hans Schmaus and Arthur Boehm (*Arch. f. Path. Anat.*, 1898, clii.). See also Schmidt's *Jahrbücher*, clviii., 94.

versal, and hematin crystals are occasionally found in the viscera. The ecchymoses occur in all parts of the body, but are apt to be especially pronounced in the mediastinum and the serous membranes. Schiff has found that in dogs, after death from phosphorus, the blood does not pass into the veins, but remains in the arteries. O. Silbermann states that thrombi are formed in the blood-vessels; and it has been shown by G. Puppe that these are very common in slow cases of the poisoning, and are of fatty nature.

It should be remembered that although some or all of the lesions which have just been described are usually found in the bodies of persons dead of phosphorus-poisoning, it is possible for the poison to take life very rapidly and leave no trace of its influence, there being not even sarcolactic acid in the urine (see case reported by Paltauf). According to the researches of W. W. Podwyssotsky, in rapid cases the first change in the body consists in the formation of little whitish-yellow necrotic foci in the liver. The anatomical changes in the liver in phosphorus-poisoning are sufficient to confirm the statements of Schultzen and Riess, that in the poisoning there is arrest of glycogen and sugar formation.

The elimination of bile acids in the urine shows that the jaundice of phosphorus is caused not by an arrest of secretion, but by an occlusion of the biliary passages and consequent resorption of the bile.\* O. Kohts has apparently demonstrated that the occlusion is most frequently due to the duodenitis involving the common duct, so as to obliterate its lumen by the swelling of the mucous membrane. In some cases, however, it is probable, as believed by Wyss, Alter, and Ebstein, that a catarrhal inflammation of the minute gall-ducts is the cause of the jaundice, and also that the result is in part effected through pressure upon those ducts by the swelling of the glandular and trabecular tissue. It is proper to state that Demarbaix and Willmart insist that the icterus is not really hepatogenous, but hemic in origin, chiefly because they have found hematinoidin in the urine. This fact, however, proves only that the blood is altered by the poison; it does not disprove the liver origin of the jaundice.

*Diagnosis.*—Acute phosphorus-poisoning so closely resembles yellow atrophy of the liver that their clinical distinction is sometimes difficult, nay, impossible. Distinct phosphorescence in the breath, vomit, or stools would, of course, be direct evidence of poisoning. This phosphorescence, however, very often cannot be detected: according to Vetter, it can be rendered more evident in the vomit, stools, etc., by acidifying with sulphuric acid and warming in a shallow dish. When death ensues during the first week of phosphorus-poisoning, the enlarged liver affords a distinctive proof of poisoning; but when the case is more protracted, the atrophied liver of phosphorus cannot be distinguished from that of the natural disease. Phosphorus-poisoning usually develops more abruptly than does acute yellow atrophy, and the primary disturbance of the stomach is more severe, while the lull of the symptoms is more complete. The clinical differences, however, between various cases of either affection are greater than those which have been relied upon as separating the two affections. Köhler has asserted that oxymandelic acid in atrophy of the liver replaces the sarcolactic acid of phosphorus-poisoning, and

\* E. Stadelmann (*Archiv f. Exper. Path. u. Pharm.*, 1888, xxiv.) states, as the result of his experiments made upon dogs, that so far as the secretion of bile is concerned three stages can be made out. In the first stage there are irritation of the liver and increase of the formation and excretion of biliary coloring-matter; in the second stage the gall becomes mucous and cloudy, and the production and separation of biliary coloring-matter are lessened (it is in this stage that the icterus begins); in the third stage the gall becomes again clear, dark, and more rich in biliary coloring-matter, so that the normal excretion of biliary coloring-matter is notably surpassed.



stress has been laid upon the asserted facts that in the natural disease leucin and tyrosin are present in abundance in the urine, while in the poisoning they are absent. In yellow atrophy, however, tyrosin is not infrequently absent from the urine and leucin present in very small amount, while both principles may be present in phosphorus-poisoning.\* In regard to the acids in the urine, very careful chemical analysis would in any case be necessary to determine their presence, and sufficient evidence is certainly not yet forthcoming to show that either of them is really characteristic. Chemical examination is therefore absolutely necessary in all medico-legal cases.† According to M. Poulet, phosphorus is eliminated as hypophosphoric acid, and the poisoning can be recognized by heating the urine with nitric acid to calcination. If hypophosphoric acid be present, as dryness is reached the mixture suddenly bursts into a flame like a packet of matches.

The cause of death in phosphorus-poisoning is probably the wide-spread structural alterations, as the experiments of A. Hauser indicate that the poison does not act by inhibiting life processes.

In the very acute cases of phosphorus-poisoning a primary condition of pronounced cardiac weakness, passing into paralysis, may be present (Pal); in the subacute cases the heart-muscle undergoes so much degeneration that a slowly developed but progressive cardiac weakness is produced and may be the cause of death.

*Treatment.*—The indications for treatment in phosphorus-poisoning are very evident. It is plain that no medication can influence the terrible organic lesions induced, and that the primary object must be to prevent the absorption of the poison. Emetics and purgatives are, therefore, of prime importance. The necessity of the persistent use of evacuants is shown by the finding of phosphorus by Starck in the stools three and a half days, and in the vomit two days, after the ingestion of the fatal dose. As phosphorus is soluble in oils, *no fatty matters* should be allowed either in the food or in the medicines. The most valuable antidotes are copper sulphate and potassium permanganate. As an emetic, *copper sulphate should always be chosen.*

The oil of turpentine, originally proposed by Andant as an antidote to phosphorus, has been largely used by experimenters, with apparently contradictory results, which, as is now known, were due to the employment of different varieties of the oil.

Ordinary American oil of turpentine and Canada balsam are of *no value* in phosphorus-poisoning.

There are in European commerce three varieties of turpentine,—the rectified, the German, and the French. Jonas found that, while the pure oil has no effect upon phosphorus, the acid French oil forms with it a crystalline, spermaceti-like mass. This is soluble in ether, alcohol, and alkaline solutions, and has received the name of *turpentine-phosphoric acid*. It is said to be eliminated by the kidneys

\* Cases (*Wiener Med. Presse*, 1872; *Schmidt's Jahrb.*, clxix. 127, cxv. 123). Ossikovsky believes that the principles appear habitually about the sixth day of the poisoning, when the liver is still enlarged.

† For discussions of the diagnosis between yellow atrophy and phosphorus-poisoning, see Köhler (*Syd. Soc. Year-Book*, 1870, 455), Schultzen and Ries (*Annalen des Berlin. Krankenhauses*, 1869, xv.), and especially I. Ossikovsky (*Wien. Medizin. Presse*, 1872, xiii., abstracted in *Schmidt's Jahrb.*, cliv. 15). For cases in which the question was legally raised, investigated, and discussed, see *Schmidt's Jahrb.*, cxli. 167; *Syd. Soc. Year-Book*, 1832, 430; *Annales d'Hygiène*, Jan. 1869.

unchanged, and to exert no deleterious influence. The elaborate experiments of Vetter on dogs and rabbits gave results in accord with these facts, for he found the rectified and German oils to be of no value in phosphorus-poisoning, while the crude acid French oil was distinctly antidotal. Kochler, however, asserts that when the German oil has not been rectified for some time, it acts upon phosphorus. He believes that the oil acts partly by oxidizing the poison and partly by converting it into the harmless turpentine-phosphoric acid. One part of the oil must be given for 0.01 part of the phosphorus.\* See also Bène.

As was pointed out by Eulenburg and Guttman, and subsequently by Bamberger, phosphorus in a solution of a soluble salt of copper becomes immediately black, owing to the formation of a phosphide of the metal. Bamberger also asserts that, while this change is very rapid, that induced by turpentine is a slow one, and, from an elaborate series of experiments upon animals, concludes that copper is much the more valuable and certain antidote. Antal appears to have been the first to use potassium permanganate as an antidote to phosphorus, and in a series of experiments upon dogs E. Q. Thornton found it much superior to cupric sulphate. Hydrogen dioxide appeared in Thornton's experiments to be valueless. In human poisoning cupric sulphate should be given in dilute solution, three grains every five minutes until vomiting is induced. After this the potassium permanganate should be freely administered, or, as was successfully done by Hajinos, the stomach may be washed out with its solution; later, the magnesium sulphate or citrate may be given as a quickly acting purge, and symptoms met as they arise.†

*Chronic Poisoning.*—Match-makers and other artisans who are exposed by their occupations to the fumes of phosphorus suffer from chronic poisoning, which is especially distinguished by the occurrence of necrosis of the upper or lower jaw. It occurs chiefly in those artisans who have bad teeth, and the experiments of Wegner have demonstrated that the necrosis of the jaw is due to the local action of the vapor of phosphorus.‡

Wegner found that when rabbits were kept in an atmosphere full of the fumes of the poison no necrosis ever occurred, unless, by means of an unsound tooth or an artificial wound, the atmosphere had access to the bone. If such access were, on the other hand, allowed to any bone of the body, periostitis and subsequent necrosis resulted. Further, when rabbits received continuously small doses of the phosphorus by the mouth, no necrosis occurred even after wounds which laid bare the bones.

**Administration.**—The dose of phosphorus may be set down as from the one-hundredth to the one-fiftieth of a grain (0.6–1.3

\* For a case of recovery see *Guy H. R.*, xxvi, 13.

† We have allowed the text to stand as in the old edition because of the present uncertainty as to the comparative values of the use of copper sulphate and potassium permanganate. In the United States phosphorus-poisoning is very rare: we have not met with more than one or two reported cases. In Continental Europe, however, probably on account of the difficulty of obtaining poisons through the restrictions of the law, phosphorus is perhaps the most used of any poison for the purpose of suicide. Thus, out of forty cases of attempted self-murder, brought to the Prag clinic between 1889 and 1895, in thirty-nine the phosphorus contained in the heads of matches had been employed (Fr. Lanz, *Berl. Klin. Wochenschr.*, 1895, xxxiii.). Formerly the treatment at the clinic consisted in washing out the stomach with warm water until the smell of phosphorus disappeared; then continuing the washing with water containing copper sulphate and calcined magnesia, and following up by giving internally copper sulphate and oil of turpentine; also large doses of sodium bicarbonate. Since 1893, when the Antal method was introduced, the plan has been to wash out the stomach with large quantities of one-eighth-per-cent. solution of the permanganate; then administer one litre of the one-half-per-cent. solution, at the same time giving a purgative; on the following day giving large doses of sodium bicarbonate with the oil of turpentine. The mortality per cent. of the cases before the change of treatment was 36.6; since the change of treatment, 41.6—a result which is not favorable to the newer method.

‡ In the manufacture of matches, phosphorus sesquisulphide,  $P_2S_5$ , has been largely substituted for yellow phosphorus, and is believed to be only slightly toxic. For a study of it, see C. G. Santesson (*V. V. N. K. I. M.*, July, 1902).

Milligm.), increased unless gastric disturbance is produced. J. A. Thompson affirms that he has given one-fourth of a grain every four hours without injury. Anstie says that he has seen slight poisoning produced by three-fourths of a grain taken in seven days in divided doses. It is always wiser to have a freshly made preparation, as phosphorus in solution or in pill is very prone to undergo oxidation.

*Zinc Phosphide* has been largely used, with asserted good results, as a substitute for phosphorus. According to the researches of Vigier, it would seem that the phosphide yields its phosphorus within the economy, probably to form a phosphuretted hydrogen. He found that it killed rabbits more quickly than did a corresponding dose of phosphorus, and that both symptoms and lesions were identical in the two cases. The phosphide should be given in pill or granule. Dose, one-twentieth to one-twelfth of a grain (3-5 Milligm.).

### ARSENIC.

Metallic arsenic is not employed in medicine. The substance ordinarily referred to as arsenic in medical parlance is arsenous anhydride,  $\text{AsO}_3$ , known officially as arsenic trioxide. This substance, which is sometimes incorrectly known as arsenous acid, is obtained as a by-product in smelting, from certain European ores, notably the cobalt ores of Germany and the iron ores of England. It occurs either as transparent glass-like pieces or in the form of a white crystalline powder. It is slightly soluble in water, requiring at ordinary temperatures from thirty to one hundred parts of water, according to various conditions, to dissolve it. It is odorless and almost tasteless, but when heated it emits a garlicky odor owing to its first being reduced to a metallic state and then volatilized.

Besides the anhydride, the U. S. Pharmacopœia recognizes the iodide of arsenic and also sodium arsenate, and a solution of potassium arsenite. *Arsenic iodide* is an orange-red crystalline powder soluble in twelve parts of water, which is decomposed by light. It is comparatively rarely employed. *Sodium arsenate*,  $\text{Na}_2\text{HAsO}_4$ , when dry, is an amorphous white powder freely soluble in water, odorless and with a faintly alkaline taste. It takes up seven molecules of water and forms colorless transparent crystals.

#### Official Preparations:

Arseni Trioxidum.....	$\frac{1}{80}$ to $\frac{1}{20}$ grain (1-3 Milligm.).
Arseni Iodidum.....	$\frac{1}{20}$ to $\frac{1}{10}$ grain (3-6 Milligm.).
Sodii Arsenas.....	$\frac{1}{12}$ to $\frac{1}{6}$ grain (5-10 Milligm.).
Sodii Arsenas Exsiccatum.....	$\frac{1}{20}$ to $\frac{1}{10}$ grain (3-6 Milligm.).
Liquor Acidi Arsenosi (1 per cent.).....	5 to 10 minims (0.3-0.6 C.c.).
Liquor Sodii Arsenatis (1 per cent.).....	5 to 10 minims (0.3-0.6 C.c.).
Liquor Potassii Arsenitis [Fowler's Solution] (1 per cent.).....	5 to 10 minims (0.3-0.6 C.c.).
Liquor Arseni et Hydrargyri Iodidi [Donovan's Solution] (1 per cent. each of Arsenic and Mercuric Iodides).....	3 to 5 minims (0.2-0.3 C.c.).



**Physiological Action.**—*Local Action.*—When in concentrated form arsenic is a powerful though slowly acting escharotic, and even when well diluted is a violent irritant. Although a violent poison to all forms of life, it acts proportionately so much more powerfully upon the higher than upon the lower organisms that it cannot be classed among the practical germicides. Johannsohn and Schaefer and also Boehm state that it exerts no influence upon non-organized ferments, either vegetable or animal, such as amygdalin, pepsin, and pancreatin.

*Absorption and Elimination.*—Although when arsenic is taken into the stomach in lumps it may be absorbed so slowly as to escape in part through the alimentary canal, when it is taken in powder, and especially when it is in the form of the soluble salt, it is absorbed with rapidity.

It is eliminated chiefly by the kidneys, but it is thrown off freely when in toxic amount by all the excretory glands and mucous membranes, especially by those of the gastro-intestinal tract. The single dose escapes rapidly from the body, elimination being usually complete in from a few hours to three or four days. When in large amount it may remain long in the body.

It is so readily taken up that its free external use and its employment as an escharotic are accompanied by distinct danger. Six cases are on record in which severe or fatal poisoning has been produced by the introduction of it into the vagina.\*

M. G. Bouchet and Lewald in independent researches found arsenic in notable quantities in the milk of nursing women.† Unterberger has detected it in the alimentary canal of animals poisoned by injection into the vein. M. Chatin has found it in the serosity of a blister, Bergeron and Lemaître in the sweat, and Taylor in the contents of the stomach of a child poisoned by its application to its scalp.

Flandin and Danger failed, three days after the last dose, to detect arsenic in the bodies of animals to which fifteen grains had been given daily; and in a child killed in two days by an arsenical pigment, none of the metal could be found in the body. In the great majority of instances, however, there is no trouble in finding arsenic in the bodies of those poisoned by it, and Steinhäuser reports a case in which it was detected in the remnants of a corpse that had been buried for twenty-two years. Further, it would appear that the failure to find arsenic has often depended upon the lack of delicacy in the chemical operations. Using the chemical method devised by Charles R. Sanger, E. S. Wood has been able to detect arsenic in the urine ninety-three days after the taking of a single toxic dose, and from sixty to eighty days after mild courses of Fowler's solution.

*General Action.*—As arsenic is never used in medicine for an acute effect, the chief interest to the therapeutist centres around its physiological action when given in small doses; yet it seems necessary here to take cognizance of the physiological action of large amounts of the poison.‡

\* See A. Haberda (*Wien. Klin. Wochenschr.*, 1897, x. 9, 201).

† See *American Practitioner*, 1887.

‡ The theory of Binz and Schulz, that arsenous acid acts by taking from protoplasm oxygen, so as to be converted into arsenic acid, and afterwards yields this oxygen to oxidize the protoplasm, and then repeats the process, seems to be so illy supported that in regard to it the reader is simply referred to *Arch. f. Exper. Path. u. Pharm.*, xi., xiv., xxxvi., xli.; also *Brit. Med. Journ.*, 1882, ii. 1135. Dogiel's theory, that arsenic unites chemically with the albuminous principle, is more probable. (See *Trans. International Congress*, 1884, i., 134.)

*Nervous and Muscular System.*—Arsenic acts powerfully upon the nerve-centres, and to a distinctly less extent upon the nerve-trunks.

In the frog arsenic acts as a paralyzant of the nerve-centres. W. Sklarck, of Berlin, states that the small dose causes in the frog cessation of voluntary movement, with complete loss of sensibility to chemical and mechanical irritants at a time when the animal will struggle actively to recover its position if laid upon its back. Tying of the iliac artery had no effect in preserving motion or sensibility in the protected leg. It would appear, therefore, that the cessation of voluntary motion was due to a complete paralysis of the centres of common sensation, probably up to the perceptive centre in the brain; the frog, placed upon his back, being induced to struggle into the normal position by sensations received either through the special senses or possibly through the muscular sense. The researches of Ringer and Murrell upon frogs yielded very different results from those just described, they found that the symptoms of poisoning came on only after the lapse of some hours, and that paralysis of voluntary motion preceded that of sensation and reflex action. Ringer and Murrell suggest that these differences of result depend upon the time of year at which the frog was experimented on.

*Circulation.*—The toxic dose of arsenic greatly lessens the rate and force of the pulse-beat and markedly lowers the blood-pressure. Sklarck found that in the isolated frog's heart arsenic produces slowness and feebleness of pulsation, ending in a diastolic arrest, after which immediate galvanic or mechanical irritation caused imperfect systolic movements. It would appear, therefore, that the toxic dose of arsenic is a direct cardiac depressant; but as both Cunza and Unterberger have found that in arsenical poisoning the heart persists in its movements after the cessation of respiration, it is evident that arsenic is more powerful as a respiratory than as a circulatory poison. Further, as demonstrated by Unterberger, the lowering of the arterial pressure in arsenical poisoning is largely due to a vaso-motor paralysis.

Thus, Unterberger found that in an animal under the influence of the poison neither galvanization of a sensory nerve nor of the vaso-motor centre in the upper cord had any influence upon the force of the blood-current. Galvanization of the splanchnics had no effect upon the arterial pressure,—apparently showing that the vaso-motor palsy was peripheral; but Unterberger found, to his astonishment, that stimulation of the cervical sympathetics had the usual effect upon the vessels of the rabbit's ear. Supposing these observations to be correct, there are only two seemingly possible methods of reconciling them: either the drug acts upon the peripheral vaso-motor nerves in the abdomen and not upon the same nerves in the neck, or else there is during arsenical-poisoning such depression of the power of the cardiac muscle that narrowing of the blood-path does not have the usual effect. Unterberger found that compression of the abdominal aorta was followed by a great rise of pressure, and therefore he believes that the heart in arsenical-poisoning has not lost its power. Some complicated transfusion experiments which he made indicated differently; so that while his proposition that arsenic paralyzes the peripheral vaso-motor nerves of the abdomen and not those of the head may be considered probable, it certainly is not proved. It would be a very easy matter to decide the question by dividing the splanchnic nerves in a poisoned animal: if the reduction of the arterial pressure be really due to an abdominal vaso-motor paresis, section of the splanchnic should have no effect on it.

*Tissue-Change.*—Schmidt and Stürzwage believe that arsenic markedly influences tissue-change, because they found in rabbits a

decided diminution in the excretion of carbonic acid and of urea during the use of minute doses of the poison. Fokker, however, was unable to perceive in three experiments that daily doses of from .15 to .075 grain of arsenic to a dog had any effect upon the elimination of urea, and Kossell and Gaethgens, in two experiments, have noted a very decided increase of the elimination of urea produced by toxic doses of arsenic in the dog. The experiments of Chittenden and Cummins are in accord with the early results of Stürzwage, as they found that in the case of rabbits *arsenous acid* has a tendency to diminish the elimination of carbonic acid. The evidence which we have at present is not sufficient to warrant a positive opinion, but it indicates that *small doses of arsenic check tissue-change and decrease nitrogenous elimination, while large toxic doses have the opposite effect.*

**Blood.**—As arsenic is frequently used in various forms of anemia much interest is attached to its effect upon the formation of blood-corpuscles. Stockman and Charteris have found that repeated small doses of arsenic cause an increase in the formation of the leucoblastic cells of the bone marrow, with consequent stimulation of the formation of white blood-corpuscles, but without marked change in the number of red cells. Larger doses produced a hyaline degeneration of the bone marrow with a decrease in the number of both white and red cells.

**Skin.**—The changes in chronic arsenical-poisoning, especially as shown in the epidemic which occurred in Manchester, in 1900, as the result of contaminated beer, bear out the conclusions of clinical experience, that arsenic has a marked effect upon the nutrition of the skin. According to Brook, the most characteristic changes in the skin in this epidemic were the deposit of pigment and stimulation in the growth of the epithelium, similar changes occurring also in the modified dermal tissues, such as the finger-nails.

**Action of Small Doses.**—Minute quantities of arsenic may be given for a long time without perceptible effect. When the dose is increased, active manifestations of gastro-intestinal irritation may appear, such as loss of appetite, nausea, abdominal pain or uneasiness, diarrhœa, and perhaps sympathetic headache. By the use of frequent small doses these symptoms may generally be avoided, and what may be termed the constitutional action of arsenic be obtained. The earliest sign of this is generally a puffiness about the eyes, at first visible only in the early morning, but soon increasing into decided œdema, which after a time may lose its local character and general anasarca develop. This anasarca, as was, we believe, first pointed out by S. Weir Mitchell, may or may not be preceded or accompanied by the presence of albumin and of tube-casts in the urine. Beyond the production of the symptoms spoken of, arsenic should never be pushed in medicine.

**Therapeutics.**—When arsenic is administered in small repeated doses, it may act as a stomachic, by slightly irritating the stomach and thereby provoking an appetite; and in certain cachexias it



increases the muscular strength and the general vigor. The history of arsenic-eating indicates that the drug has some positive tonic influence over nutrition; and although the increase of strength and of blood caused by its use in cachexias may be due to some indirect action of the drug,—for example, to a removal or overcoming of the morbid agent of the disease, and a consequent allowing of the recuperative powers of the system to assert themselves,—there is much reason for believing that the drug does act as a direct stimulant to nutrition. All that we know of the effect of arsenic upon the system throws only enough light on its therapeutic action to enable us to class it as an alterative,—a modifier and often an improver of nutrition.

After very much discussion\* it seems to be established that many of the Styrian peasants use arsenic habitually in large quantities; the young girls to beautify their complexions and enhance their charms; the men with the belief that it will increase their “wind,” endurance, and sexual powers. The best authorities state that the arsenic-eating is practised chiefly in the northern and northwestern parts of Styria: that the white arsenic is preferred, the yellow commercial article being sometimes taken; the native red arsenic, or orpiment, very rarely; and that the commencing dose is about 0.22 grain, which is very slowly increased to 0.62 grain *avirdupois*.†

Among the diseases which clinical experience demonstrates are especially benefited by the use of arsenic is *chronic malaria*. No one would at present think of employing the drug in acute *remittent fever*, or even in acute *intermittent*, unless under very peculiar circumstances. It is in those cases which have resisted quinine, in which the paroxysms have become irregular, returning at long intervals, and in which the anemia and the general nutritive disturbance are even more prominent than the febrile disorder, that arsenic is especially valuable. In these cases it should be administered with sufficient boldness, very generally in conjunction with iron. George B. Wood recommended that the first doses should be as large as the system will endure, so as to make a decided impression at once. When the ague paroxysms are frequent it is perhaps well to employ this plan; but when it is the cachexia rather than the active disorder that is to be combated, it is preferable to commence with small doses and to increase them until some constitutional symptom is produced. In ordinary *intermittents*, after the paroxysms have been broken up by quinine, it is very well to place the patient upon a preparation of arsenic and iron, as a prophylactic against their return. When, in ordinary *intermittent fever*, for any cause quinine cannot be administered, arsenic may be employed. In these cases, as already intimated, the first dose should be large, so as to make an immediate

\* See Yost (*Lehrbuch der Pharmacodynamik*, Aufl. iii. i.), Charles Heisch (*Pharm. Journ. Trans.*, 1859 and 1860, i. 556; *British and Foreign Med.-Chir. Review*, xxix. 144), and C. MacLagan (*Edinb. Med. Journ.*, 1864, 203; *Edinb. Med. and Surg. Journ.*, 1871, xvi. 569).

† The experiments of Cloetta (*A. E. P. P.*, liv. 196) indicate that the tolerance to arsenic is based on impeded absorption. In the dog, which has developed high resistance to arsenic given by mouth, the susceptibility to the metal, injected hypodermically, is not diminished.

impression; from five to ten minims of Fowler's solution, properly diluted, may be given every two or three hours until some decided symptom is produced. When the stomach refuses the remedy, it has been recommended by Boudin to give it by the rectum, which he affirms will often bear even a grain of the acid. Not more than a third of this amount should, however, be used as a commencing dose. In *malarial intermittent neuralgia*, arsenic may be employed as a very useful adjuvant to the antiperiodic alkaloids. K. M. Downie calls attention to the value of arsenic as a *prophylactic* against malaria. His trials were not numerous enough to be conclusive, but so far as they go they indicate that arsenic is even superior to quinine.

It is alleged that arsenic injected directly into the growth is an effective remedy in *lymphatic tumors*, especially in the affection known as *malignant lymphoma*.\*

In various skin diseases arsenic is a valuable remedy. According to Duhring it affects the epidermis generally by its influence upon nutrition. It is more commonly useful in those skin diseases involving the superficial strata of the integument. As it is a stimulant it should ordinarily not be employed in the acute inflammatory stages of skin disease, when there is burning, itching, and rapid cell change. Its greatest use in skin diseases is in the chronic conditions, as in *psoriasis* and in *eczema*, especially of the chronic squamous and papular varieties, and where the disease is superficially seated.

*Pemphigus* is generally favorably influenced and often relieved or cured by its use. It should be prescribed cautiously but fearlessly, large doses usually being required. It is the most reliable remedy for this disease. In *lichen* it is usually employed with great advantage, especially in *lichen planus*, in the rare *lichen ruber* of Hebra, and in allied diseases. Occasionally it may be given with benefit in chronic *urticaria*.

It may prove of value in certain cases of *acne* and *comedo*, especially in chronic small papular *acne*, in neurotic cases. In certain glandular hypersecretory diseases, as *seborrhæa* and *hyperidrosis* of neurotic origin, it is also useful. Before prescribing it the digestive tract should be carefully looked into, and if disordered in the slightest degree should first be rectified. This observation holds good for its use in all diseases of the skin. In *morphæa*, *alopecia areata*, and other atrophic diseases it is also sometimes of value. If improvement follows its use it is usually best to allow the patient to continue with the treatment for some time after all symptoms of the disease have disappeared.

Arsenic is a very valuable remedy in the treatment of chronic *bronchitis*, and is often of the greatest service not only in chronic *pneumonia*, or so-called *fibroid phthisis*, but even in true *tubercular phthisis* when the course is very slow and chronic. In *asthma* it may be given internally and also used locally. (See EXPECTORANTS.)

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\* See *Wien. Med. Wochenschrift*, 1871; *Archiv f. Klin. Chir.* xviii.; *Stricker's Jahrb.*, 1877.

In certain nervous diseases arsenic acts very favorably, in some unknown way. In *chorea* it has acquired a deserved reputation. In this affection iron and other tonics are generally indicated and may be given consentaneously with the arsenic. It is best, however, to administer the latter separately, as the dose must be steadily increased until œdema or other manifestations betray a decided action. Arsenic has from time to time been strongly recommended in *whooping-cough*, non-malarial *neuralgia*, and simple *gastralgia*, or *gastric neuralgia*.

Arsenic is of value in those forms of *chronic rheumatism* in which potassium iodide is commonly employed. It is often advantageous to alternate, administering one of these alteratives for three or four weeks, and then the other for the same length of time. In *rheumatic gout*, or *rheumatoid arthritis*, it has been highly extolled.

**Toxicology.**—When a single dose of arsenic of just sufficient size to be felt is ingested, colicky pains, diarrhœa, and perhaps nausea result. After a very large toxic dose, in from one-quarter to three-quarters of an hour an intense burning pain is felt in the œsophagus and stomach, soon spreading to the whole belly, and often accompanied by a sense of constriction at the throat and an acrid, metallic taste. In a very short time violent vomiting and purging come on. The matters rejected are at first mucous, and variously colored by the contents of the *primæ viæ*; but they soon become bilious, often yellowish or greenish, and finally serous, with mucoid flakes and a greater or less amount of blood. As the case progresses the symptoms mentioned increase in intensity, and to them are soon added others of different nature. The thirst is excessive; the urine is suppressed; the extremities are icy cold; the pulse is small, feeble, and frequent; the rapid and labored respiration is very much embarrassed and painful from the abdominal tenderness; the surface is dark and cyanosed; violent cramps add their torture; exhaustion deepens into collapse; convulsions or coma ensue, and death occurs in from five to twenty hours.

In another set of cases, when the dose has been smaller, or the subject less susceptible, the termination is not reached so soon. After symptoms, similar to but less violent than those just described, have lasted from a few hours to one or two days, a remission occurs; the purging and vomiting grow less frequent, or perhaps intermit; even the abdominal tenderness may in great measure disappear; but the persistent thirst, cold extremities, and albuminous urine show that the danger is not past, and after a time the case puts on a more alarming aspect. Fever develops, the tongue becomes dry and red, the belly very tumid, the abdominal pain more severe, dyspnœa and cyanosis occur, the face is swollen, nervous symptoms, tremblings, cramps, and convulsions appear, and finally an icy coldness pervades the frame, and death occurs in from two to six days. The mind is generally clear to the last. An eruption very frequently appears.



sometimes as early as the second day, sometimes not until the fifth. Its character is various: thus, it may be petechial, urticaria-like, papular, vesicular, or pustular.\*

Such are the ordinary phenomena of acute arsenical-poisoning; but anomalous cases are not very rare. Immediate profound collapse, without abdominal pain, is said to have been the chief manifestation in some cases. We have seen heavy sleep as the most marked symptom, the sleep, however, being interrupted at intervals by wild outcries and writhings, evidently the outcome of abdominal pain, although no statement could be obtained from the patient. Again, serous purging may be the chief symptom, and arsenical-poisoning has been mistaken for cholera, not only during life, but also on the post-mortem table.†

When arsenical-poisoning is not fatal the convalescence is apt to be slow and interrupted by various disorders. Prominent among these are affections of the alimentary canal, due to the structural changes produced by the poison. Nervous symptoms are common, and may affect the motor or sensory sphere separately or together. In some cases they have developed very suddenly. We have seen anesthesia of the feet as the only symptom; motor paralysis may exist alone, but it is usually accompanied by anesthesia, hyperesthesia, loss of temperature-sense, great feeling of coldness, or other disorder of sensation, and not rarely excessive pain, which may be aching or lancinating. Occasionally there are severe cramps. Normal sensibility is usually regained before normal motility. Of one hundred cases of arsenical paralysis collected by Imbert-Gourbeyre in more than half all the extremities were affected; about one-fourth were paraplegic; in the remainder there was hemiplegia or local palsy. Most frequently the paralysis was not pronounced above the elbow or knee. The lamed muscles are usually sensitive to pressure‡ and undergo rapid atrophy, losing very early their electro-muscular contractility, or presenting the "reactions of degeneration." The tendency towards more or less complete recovery is remarkable. We have seen recovery when the muscular remnants on the wasted limbs had for many months been unable to respond to any form of electric current; and out of Imbert-Gourbeyre's one hundred cases all recovered except three.

*Post-mortem Findings.*—The most obvious lesions found after death from acute arsenical-poisoning are those of severe gastro-enteritis, but often there is also a wide-spread granular or fatty degeneration of the tissues.

The gastric mucous membrane is usually swollen, maculated with patches of a deep crimson or more commonly brownish-red color, and is often softened and covered with a diphtheritic exudation, but is rarely ulcerated. Perforation is exceedingly uncommon. The mucous membrane of the upper part of the small

\* See Imbert-Gourbeyre (*Moniteur des Hôpît.*, 1857), also A. Huber (*Zeitschr. Klin. Med.*, 1888).

† See *Virchow's Archiv*, 1870, 1.

‡ Consult C. Gerhard (*Sitzungsber. Physik. Med. Gesellsch. Würzburg*, April, 1882), Renner (*Ueber ein Fall von chron. Arsenvergift.*, Würzburg, 1876), W. P. McIntosh (*N. Y. Med. Record*, Feb. 1885, 145), Seguin (*Journ. Nerv. and Ment. Diseases*, Oct. 1882, vii. 665), and O. K. Mills (*Trans. College of Physicians of Philadelphia*, 3d series, vi.; *Archives de Physiol. Norm. et Path.*, 1884, iv.).

intestine, and sometimes of the whole of it, is in a condition similar to that of the stomach. In some cases the lesions very closely resemble those of cholera, as was first pointed out by Virchow. In the microscopic examination of a cadaver whose bowels were filled with a "rice-water" fluid, that observer found in the intestinal contents epithelial flakes and the fungus described by Klebs as peculiar to, and, indeed, the cause of, cholera. The epithelial cells of the mucous membrane were choked with granules, many of them in an advanced stage of fatty degeneration; the interstitial tissue was full of large round granulated cells; the solitary glands and Peyer's patches were very much swollen. These facts have been confirmed by Hoffmann. The gastro-intestinal lesions produced by arsenic are not due solely or largely to its immediate local effect, since they occur equally when the animal is killed by injection of the poison into a vein. The local influence of the drug is, however, probably not altogether lost, since Unterberger found that a larger dose was required to kill an animal by venous injection than by exhibition by the mouth. Curious and at present unexplainable anomalies occur in the distribution of the gastro-intestinal inflammation, and autopsies have been reported in which the stomach has altogether escaped.

M. Karajau reports a case which had been mistaken during life for acute atrophy of the liver; Grohl and Mosler one in which they found fatty or granular metamorphosis of the glands and epithelium of the stomach or intestines, of the cardiac muscle, of the diaphragm, of the cortical portions of the kidney, and, to a slight extent, of some of the voluntary muscles; I. I. Pinkham one in which the liver, kidneys, and epithelial lining of the peptic glands were almost destroyed; similar lesions have also been reported by M. V. Cornil and by Féréol.

As was first pointed out by Salkowsky when animals are poisoned by a small dose of arsenic, so as to live from three to six days, the liver\* becomes much enlarged and very fatty. On microscopical examination, the cells on the exterior of each acinus are natural; those in the centre in the most advanced stages of degeneration. The kidneys are similarly affected,—their tubes choked up with fat-globules, their epithelium almost completely destroyed. The muscles of the heart and diaphragm are also compromised.

In frogs poisoned with arsenic the epidermis peels off from the derm, as was first noted by Ringer and Murrell, and Emily A. Nunn has found that the influence of the poison is first manifested in the under portion of the epidermis, the degeneration progressing from the derm outward.

In some cases of arsenical-poisoning yellow patches, believed to be due to the formation of arsenical sulphides, have been noted on the mucous membrane of the stomach and intestines. Similar yellow deposits were found by Chumilal Bose on the endocardium. It is probable that in these cases the sulphide is formed after death by the aid of putrefactive gases.

Besides the alimentary lesions, frequently may be found, after death from arsenic, evidences of pathological changes in the central nervous system.

N. Popoff found, in dogs killed in a few hours by a dose of arsenic, the spinal cord inflamed; after slower poisoning there were masses of "exudate" in the neighborhood of the blood-vessels, and in very protracted cases the walls of the spinal arterioles were found to be thickened and the large cells of the gray matter profoundly altered. The protoplasm first became opaque and granular; the nuclei grew fainter and fainter, and disappeared; vacuoles appeared, and encroached more and more on the shrunken body of the cell, which finally melted down. In

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\* Salkowsky also noted that early in both arsenical- and antimonial-poisoning the glycogenic function of the liver is abolished. Podwyssotsky finds that the first change produced by overwhelming doses of arsenic consists in the formation of necrotic foci in the liver (*St. Petersburg Med. Woehens.*, 1888). O. Silberman believes that during life thrombi form in various portions of the body (*Archiv f. Path. Anat.*, cxvii). For further discussion see Ziegler (*Beiträge Path. Anat.*, ii.), also M. Wolkow (*Archiv f. Path. Anat. u. Phys.*, 1892, cxxvii.).

the elaborate experiments, however, of C. Alexander upon rabbits, the spinal cord was found to be healthy, but the nerve-trunks were in a condition of degenerative atrophy, and the muscles themselves had undergone changes which were believed to be the result of coagulation-necrosis.

That arsenic is capable, in man, of producing a myelitis especially affecting the multipolar cells of the cord is shown by the autopsy reported by Erlicki and Rybalkin, in which case there was no tenderness of the nerve-trunks. There appear to be, therefore, two forms of arsenical paralysis,—one due to myelitic change, the other to a wide-spread multiple neuritis,—the diagnosis between the two being made by the presence or absence of nerve-tenderness. It is very probable that in some cases both lesions are present. In some of these cases trophic changes are pronounced: thus, we have seen a growth of hair several inches long cover the wasted limbs. If in any case of arsenical paralysis there were no sensory disturbance, the probabilities would be very strong that the lesion was a toxic poliomyelitis.

We know of no general studies upon the blood of human beings poisoned with arsenic.

S. Bettelman has shown that in the rabbit in subacute arsenical-poisoning there is a marked lessening in the number of the red blood-corpuscles and in the percentage of hemoglobin, without any distinct change in the general percentage of leucocytes, although the lymphocytes increase and the eosinophile cells decrease. Late in the poisoning nucleated red blood-corpuscles may be found in the circulating blood.

The symptoms of acute arsenical-poisoning resemble so closely those of cholera nostras that without the knowledge of the taking of the poison, or chemical analysis of the excretions, a positive diagnosis may be impossible. The abdominal pain is, however, usually more severe than in the natural disease.

Death usually results in acute arsenical-poisoning in from eighteen hours to three days; but Taylor reports a case in which it occurred with tetanic symptoms in twenty minutes, and life has been protracted until the sixteenth or even the twentieth day. The effects of the arsenical solutions, such as Fowler's, are more rapid and severe than are those of the solid drug. Tardieu places the minimum lethal dose at from ten to fifteen centigrammes (1.54–2.31 grains).

W. C. Jackson records a case of recovery, under the early use of emetics, after an estimated dose of two ounces had been taken; and E. D. Mackenzie gives an account of a man who swallowed an unknown quantity of arsenic in lumps, and received no treatment for sixteen hours, yet recovered after passing per anum one hundred and five grains of arsenic in two masses. On the other hand, death has resulted from the use of very small amounts. Taylor asserts that the smallest fatal dose hitherto recorded is two grains. Lachèse affirms that six milligrammes (0.09 grain) will produce decided but not serious symptoms, and that from one to three centigrammes (0.154–0.462 grain) are poisonous, and from five to ten centigrammes (0.77–1.54 grains) fatal. The escapes from death after the ingestion of large amounts of arsenic have, without doubt, depended upon its being, as in the cases above narrated, in an insoluble form.

*Treatment.*—As arsenic in large doses generally induces vomiting, it is rarely necessary in poisoning to evacuate the stomach by artificial means. If free emesis, however, have not occurred, a prompt emetic, such as mustard or zinc sulphate, should be at once exhibited, and very generally the stomach should be well washed out by large draughts of warm water, with salt, if necessary for the return of the



water. With the emetic, or sooner, if possible, the antidote should be administered. The most certain antidote is the *freshly precipitated ferric hydroxide*, which forms with arsenous acid a very insoluble compound. The antidote must be freshly prepared, and must be given in great excess; according to the experiments of T. and H. Smith, of Edinburgh, at least eight grains of the iron being required for the conversion of one grain of the arsenous acid.

In practice, any of the official ferric solutions—that of the chloride being generally preferred, as most readily procured—should be neutralized by sodium carbonate or preferably by magnesia, and a portion of the precipitate given at once, stirred up in *hot* water. The remainder of the antidote, having been hastily washed by emptying it on to a piece of muslin or in a filter, pouring water on it and allowing it to drain, should be administered very freely, indeed indefinitely, as it is entirely harmless. H. Köhler, of Halle, has made an elaborate series of chemical, physiological, and clinical experiments upon the comparative antidotal values of the *saccharated ferric oxide* and the *freshly precipitated ferric hydroxide*. His results indicate that the former preparation is the better; but, as the efficiency of the hydroxide has been so frequently proved at the bedside, further testimony is desirable before it is superseded, especially since the other ferric preparation is not official with us, and is not so readily prepared on the spur of the moment as is its fellow. *Dialyzed iron* has been used with very good results, but it is much better to precipitate it, just before administration, with a small amount of ammonia or other alkali. *Magnesia*, freshly calcined or freshly precipitated from a solution of its salts, is an antidote of some avail in arsenical-poisoning, but is decidedly less efficient than the iron oxide.

The best form of the iron antidote is probably the *Ferric Hydroxide with Magnesium Oxide* (FERRI HYDROXIDUM CUM MAGNESII OXIDO, U. S.), *Arsenical Antidote* of the German Pharmacopœia. It is made by precipitating the solution of ferric sulphate by magnesia. In emergencies, Monsel's solution, tincture of the chloride of iron, or any solution of an iron salt, may be substituted for the tersulphate solution.

In arsenical-poisoning castor oil should be administered for the purpose of expelling the poison from the bowels, and demulcent drinks, opium, stimulants, dry external heat, and rubbing should be employed as called for by the symptoms. When there is a tendency to suppression of urine, very large draughts of feebly alkaline water should be given as frequently as the stomach will bear.

*Chronic arsenical-poisoning* is often difficult of diagnosis; the symptoms are usually both local and constitutional. When the poison has entered the system through the respiratory tract the local irritation will be shown by dryness of the throat, coughing, and other evidences of chronic bronchitis or severe laryngo-bronchial catarrh. When the poison has entered the system through the alimentary tract, loss of appetite, with frequent vomiting and violent diarrhœa, are common. The general symptoms consist of depression of spirits, irritability, insomnia, giddiness, failure of memory, sometimes marked mental failure. According to Reynolds, in the epidemic which was caused by arsenical beer, involvement of the nerve-trunks was very common. There were in these cases marked disturb-

ances of sensation, paresthesia, and partial anesthesia, although complete anesthesia was rare. There may be muscular tremors or stiffness; vertigo or other disorders of equilibrium are sometimes seen, while violent neuralgic pains, with numbness of the extremities, marked tenderness of the nerve-trunks, and other results of peripheral neuritis, are not rare. In most cases of chronic arsenical-poisoning without a history the congeries of symptoms is, however, sufficient only to arouse suspicion and to call for a chemical examination of the urine. It should always be remembered that a peripheral neuritis is usually due to the presence of some poison, and that a group of wide-spread atypical symptoms not characteristic of any distinct disease is usually either toxic or diathetic.

Sometimes in acute, more frequently in chronic, arsenical-poisoning, or as the result of long-continued medicinal use of the drug, certain disorders of the skin appear.\* Of these, herpes zoster seems to be the most frequent; it probably is the result of an arsenical neuritis. Another common skin affection is erythromelalgia, the painful red swelling of the epiderm. In protracted cases there is frequently thickening of the horny tissue in the palms of the hands and soles of the feet, which occasionally extends up the limb. The formation of transverse ridges across the nails, the result of the hyperkeratosis, has also been noted. The deposit of pigment in the skin and mucous membranes is an almost constant symptom,—while there have been noted a number of other changes in the skin, such as erythematous and desquamatus eruptions, urticaria and subcutaneous œdema, vesicular eruptions, bullæ, papules, pustules and ulcers, purpura, shedding of the hair and nails, and keratosis.

In artisans who work in copper local arsenical-poisoning is not very rare. Ulcers about the roots of the nails are generally the first trouble in these cases, but after a time eczematous or papular eruptions appear, and even subdermal erysipelatous inflammations are developed. Very commonly to these local symptoms are added, after a time, the usual phenomena of chronic arsenical-poisoning.

In the arts, preparations of arsenic are largely used as pigments;† and, excepting the manufacturers of arsenical compounds, it is almost exclusively those who are accidentally exposed to the deleterious influence of these pigments that suffer from chronic arsenical-poisoning.

\* See *Schmidt's Jahrb.*, clxv.; *Deutsch. Archiv Klin. Med.*, 1899, xliv.; *Boston Med. and Surg. Journ.*, cxviii., cxix., cxx., cxxi., cxxii.; *Ann. de Dermatol. et de Syph.*, 1897, viii. 4, 345; *Monats. f. Prakt. Dermatol.*, 1897, xxiv. 3, 137.

† For an excellent report upon this subject, see *Report of the State Board of Health of Massachusetts*, Jan. 1872, where it is stated that from five hundred to seven hundred tons of arsenical pigment were manufactured in 1862 in England alone. Fatal chronic arsenical-poisoning from working in aniline dyes is reported in *Sticker's Jahrb.*, 1877, 501. F. C. Shattuck (*Med. News*, 1893, lxii.) reports a number of cases in which the symptoms have been gastro-intestinal irritation, anemia, dermatitis, redness of the conjunctiva, puffiness under the eyes, headache, irritation of the upper air-passages, albuminuria with casts and blood, and peripheral neuritis. The number of cases of chronic arsenical-poisoning detected in and about Boston, contrasted with the rest of the world, is something remarkable, and is scarcely to be accounted for by the alleged superior acuteness of the Boston physicians. A further difficulty of the subject is that arsenic has been detected in the urine of many normal Bostonians.

The poisonous colors are of various hues, and, being very cheap, and remarkable for their purity of tone and their permanence under exposure to light, are much used by paper-makers. *Scheele's Green*—copper arsenite—contains fifty-five per cent., by weight, of arsenous acid; and *Schweinfurt Green*—the aceto-arsenite—fifty-eight per cent. The arsenical dyes are not all green, but may be in almost any hue; they are largely due to the use of arsenic in the manufacture of magenta and other aniline colors. E. S. Wood, of Harvard, has shown that in different parcels of the same goods one will contain arsenic and the other not, because the aniline dyes are sometimes contaminated with arsenic and are sometimes free from it. These poisonous colors are by no means confined to wall-paper. Sweetmeats have been colored with them; pasteboard boxes, artificial flowers, tarlatan dresses, India muslins, cretonnes, walls of dwellings, shelves of groceries, toys of children, and various other articles have been made the vehicle of death, so that hundreds of cases of poisoning have resulted from the use of these pigments, which ought to be banished by the strictest laws. In most cases it is probably the minute dust, which is separated mechanically and diffused through the room, that produces the fatal result; but poisoning has occurred when the arsenical paper was covered over with another paper. Hambers has made elaborate chemical researches upon the air of these apartments, and believes that he has demonstrated that some arsenic escapes in the form of arseniuretted hydrogen. Not rarely the poison has been taken directly into the stomach, especially by children.

The chief indications in *chronic arsenical-poisoning* are to remove the patient from the exposure and to treat symptoms as they arise.

*Post-mortem Imbibition.*—Owing to the extensive use of embalming with liquids made either directly from arsenical preparations or from commercial chemicals which habitually contain arsenic as an impurity, it is becoming extremely difficult in criminal legal practice, as it occurs in the United States, to prove death from arsenical-poisoning. Although the subject is somewhat aside from the main *motif* of the present volume, its importance seems to require a brief authoritative consideration, the details of which may be found in recent works on toxicology. The old belief that the finding of arsenic in the brain or organs distant from the abdomen was proof that the poison had been administered during life, and had been scattered by absorption\* and not by imbibition, is absolutely incorrect.

The qualitative distribution of arsenic in the body is of very little service in most cases in determining the question as to whether the poison has been given before or after death. Arsenic which has been injected into the thorax or into the abdomen, after death, may be found subsequently in the brain and other distant parts of the body. More respect should be given to the quantitative distribution of arsenic. It is naturally to be expected that more arsenic should be found in the parts adjacent to the points of injection than in distant portions of the body; and that the position of the body, through the force of gravity, should influence the distribution of the poison. Thus, if the corpse has lain upon the back more arsenic should be found in the back tissues than in those in the upper portions of the body; if on the left side more poison should be found in the left than in the right kidney. Nevertheless, when a body has lain for many weeks after post-mortem arsenicalization the laws of diffusion assert themselves against the law of gravity.

To be of any value whatever the quantitative chemical study of the different organs must have been made with the greatest care and attention to details, not only chemical but also physical. The whole organ must have been used or reduced to a common pulp, a portion of which has been analyzed. Moreover, the quantitative differences must be most pronounced or, as it has been well stated by Mann, "must be absolute not relative; the left kidney must contain arsenic and the right none; it is not enough that the right kidney shall contain less than the left; such a difference is compatible with vital absorption."

\* In this paragraph the word "absorption" is used technically to indicate the taking up of the poison during life; "imbibition" to indicate the passage of the poison from tissue to tissue after death.



Except under rare circumstances, as when the body has been buried only a few days after embalming, so that there has not been time for the processes of imbibition to carry the poison throughout the organs, the expert is not justified in asserting from quantitative evidence that the poison has been taken during life; the imperilling of life by overconfidence of statement is not a rare crime in American courts. To-day is as true as ever the dictum of Witthaus and of Torsellini, that it is impossible in most cases to distinguish with positiveness by chemical analysis between absorption and imbibition, or, in other words, whether the poison has been put into the body before or after death.\*

**Administration.**—The beginning dose of arsenic is one-thirtieth of a grain (0.002 Gm.), which should be given in pill *after* meals, and be slowly increased until a perceptible influence, or the desired therapeutic effect, is obtained. In many cases (*chorea*, *lymphoma*, *intermittent fevers*, etc.) it is necessary to push the remedy until decided evidences of poisoning are secured: in this case a liquid preparation should be selected.

**CACODYLIC ACID.**—Cacodylic acid is chemically di-methyl-arsenic acid. Several of its salts have been employed in medicine as substitutes for arsenic. It has been claimed for these preparations that they are much less poisonous than the ordinary arsenical preparations, and can be used freely without danger of causing unpleasant symptoms. It would seem that their low degree of toxicity depends upon the fact that the arsenic is so firmly bound up in the composition that it is liberated in the body only in very small quantities, since the experiments of Heffter indicate that only about two or three per cent. of sodium cacodylate is destroyed in the body and eliminated as arsenic. It is therefore probable, as claimed by Heffter, that the cacodylate is not active as such but only through the liberation of free arsenic. This view is also held by Fraser, who has used the remedy in a number of cases of *chorea*, *eczema*, *leukemia*, and *chlorosis* without special result. The remedy has been especially lauded by Gautier, who has employed it in various forms of *tuberculosis* with asserted good results. Sodium cacodylate has been used as a substitute for arsenic in all the conditions in which this remedy is useful, in doses of one-quarter to one grain (0.016–0.06 Gm.). In *chlorosis* and other forms of anemia the cacodylate of iron is preferred, and may be given in the same dose. According to Gautier it is always preferable to give the remedy subcutaneously. Under these circumstances a five-per-cent. solution may be employed, of which 15 minims (1 C.c.) may be given at a dose.

**ATOXYL.** *Meta-arsenic-anilid.*—This is a white, odorless powder, soluble in twenty per cent. of hot water, and containing thirty-seven and six-tenths per cent. of metallic arsenic. According to Blumenthal it is forty times less poisonous than arsenic acid, but as its physiological, toxic, and remedial properties are probably in direct proportion to the amount of arsenic eliminated in the system, it does not seem probable that it has any advantage over the older preparations of arsenic. It is claimed, however, to lend itself especially well to hypodermic medication; according to Schild, three to fifteen minims of the twenty-per-cent. solution may be given hypodermically for five days, subsequently on alternate days. Schild believes that it is especially liable to act upon the heart, and considers cardiac weakness a contraindication to its use.

## MERCURY.

Metallic mercury in its ordinary form is almost incapable of absorption, but when finely subdivided by trituration with inert substances

\* American readers see especially *Medical Jurisprudence and Forensic Medicine and Toxicology*, by Witthaus and Becker. Also *Text-book of Legal Medicine and Toxicology*, by Peterson and Haines. Also *Forensic Medicine and Toxicology*, by Dixon Mann.

it becomes capable of penetrating the mucous membranes. Preparations containing metallic mercury which are recognized by the U. S. Pharmacopœia are: the mass, the ointment, and mercury with chalk. Mercury is capable of acting either as a univalent or as a divalent base, consequently it forms two series of salts, the mercurous and the mercuric. The Pharmacopœia recognizes of the salts of mercury,—two chlorides, two iodides, two forms of the oxide, an oleate, and a complex body resulting from the precipitation of solution of corrosive sublimate by ammonia known as ammoniated mercury.

*Mercurous chloride* or calomel (*hydrargyri chloridum mite*), occurs as a white crystalline powder, insoluble in water, alcohol or ether. *Mercuric chloride* or bichloride of mercury, more commonly known as **corrosive sublimate** (*hydrargyri chloridum corrosivum*), is in colorless crystals, soluble in thirteen parts of water and three parts of alcohol, odorless, but with an acrid metallic taste

*Mercurous iodide*, or yellow iodide of mercury, is a bright yellow amorphous powder without odor or taste, practically insoluble in either water or alcohol. *Mercuric iodide*, or red iodide of mercury, is a bright-red, odorless, and tasteless powder, sparingly soluble in alcohol and practically insoluble in water; solutions of potassium iodide, however, dissolve it easily.

Two forms of the oxide of mercury are recognized, the yellow and the red. In their chemical relations these two preparations do not differ. They are both insoluble in alcohol and in water. The yellow is amorphous and of a light orange yellow color. The red oxide is composed of orange-red crystals which become yellow when finely triturated.

Ammoniated mercury is made by precipitating the bichloride with ammonia water and has the formula  $\text{HgNH}_2\text{Cl}$ . It occurs in the form of a white, amorphous powder, with a metallic taste, insoluble in water or alcohol.

#### Official Preparations :

Hydrargyrum .....	Not used internally.
Hydrargyrum Ammoniatum ...	Not used internally.
Hydrargyrum cum Creta [Gray Powder] .....	2 to 10 grains (0.13–0.6 Gm.).
Hydrargyri Chloridum Mite [Calomel] .....	{ Alterative $\frac{1}{2}$ to 1 grain (0.03–0.06 Gm.). Cathartic 2 to 10 grains (0.13–0.6 Gm.).
Hydrargyri Chloridum Corrosivum [Corrosive Sublimate] .....	$\frac{1}{60}$ to $\frac{1}{2}$ grain (1–8 Milligram.).
Hydrargyri Iodidum Flavum [Protiodide] .....	$\frac{1}{60}$ to 1 grain (0.01–0.06 Gm.).
Hydrargyri Iodidum Rubrum [Biniodide] .....	$\frac{1}{60}$ to $\frac{1}{2}$ grain (1–8 Milligram.).
Hydrargyri Oxidum Flavum ...	Not used internally.
Hydrargyri Oxidum Rubrum ...	Not used internally.
Massa Hydrargyri [Blue Mass] ..	1 to 10 grains (0.06–0.6 Gm.).
Unguentum Hydrargyri [Blue Ointment] (50 per cent.) .....	Externally only.
Unguentum Hydrargyri Dilutum (33 per cent.) .....	Externally only.

Oleatum Hydrargyri.....	Externally only.
Unguentum Hydrargyri Ammoniati (10 per cent.).....	Externally only.
Unguentum Hydrargyri Nitratis (7 per cent.).....	Externally only.
Unguentum Hydrargyri Oxidi Flavi (10 per cent.).....	Externally only.
Unguentum Hydrargyri Oxidi Rubri (10 per cent.).....	Externally only.
Emplastrum Hydrargyri (30 per cent.).....	Externally only.
Pilulæ Catharticæ Compositæ....	1 to 2 pills.

*Local Action.*—The local effect of mercurial preparations varies from complete inertness to an active escharotic influence, so that each preparation must in this regard be studied by itself.

*Absorption and Elimination.*—All the official preparations of mercury yield themselves or the mercury in them to absorption, and after absorption to elimination. The metal has been found in the blood,\* in the urine, in the serum of blisters, in the saliva, in the feces, in the pus from ulcers, in the seminal fluid, in the milk of nursing women,—indeed, in every conceivable secretion and in every tissue. Heller found it in the aborted fetuses of salivated women, and Mayençon and Bergeret in the urine of a baby whose nurse was taking calomel; and each of these observations has been confirmed by Wellander.

An enormous amount of work has been done to determine how rapidly mercury is eliminated, and whether when given internally it is all thrown out of the system. The result of all this labor seems to us to prove that the single dose of mercury does not remain in the system, but that when the drug is administered constantly for a length of time elimination does not keep pace with absorption, so that the mercury accumulates in the tissues. Moreover, the elimination takes place irregularly and intermittently, for reasons that at present cannot be made out. Further, there does not appear to be any limit of time during which stored-up mercury may remain in the body; indeed, all the evidence points to the possibility of mercury being deposited in the tissues in such form that it is practically inert and has no influence upon the system; liable, however, under certain agencies, to be set free and to exert its power upon the general nutrition.

There has been much speculation as to the exact form in which mercury is absorbed. The only official salt which is at all readily soluble in water is the corrosive sublimate. It is certainly not absorbed as mercuric chloride as it is so powerful a precipitant of albumin that it cannot exist in the system unchanged. Jeannel has found that calomel in the presence of an alkaline carbonate has decomposed and a gray oxide was formed. This gray oxide is very sparingly soluble in water but if a fatty oil be mixed with the alkaline solution a large part of the mercury is dissolved. No plausible explanation of the absorption of mercury is found in the solubility of the albuminate of mercury in the presence of the excess of albumin.

\* Gmelin (*Bull. de Thérap.*, xiii.); Salkowsky (*Virchow's Archiv*, xxxvii. 347); Mayençon and Bergeret (*Robin's Journal de l'Anatomie*, 1873); Klinik (*Detroit Med. Journ.*, May, 1877).



The theory of Mialhe that calomel is converted by hydrochloric acid in the stomach into a bichloride and as such absorbed is certainly untrue, for it has been shown that the gastric juice at least at the body temperature is not capable of forming corrosive sublimate with calomel, and if it were, corrosive sublimate, as we have seen, is incapable of being absorbed unchanged. The superstition against the administration of acid drinks, as lemonade, in conjunction with calomel, has no chemical foundation.

The rate of absorption of mercury is of course affected by the choice of preparation and by the method of administration. Wellander has found mercury in the urine fourteen hours after its application to the human skin and one hour after its subcutaneous administration. Mayençon and Bergeret found that when one centigramme of corrosive sublimate was given hypodermically to a dog, the urine for the next twenty-four hours contained mercury, afterwards none. When a centigramme was given daily for ten or twelve days, the urine contained mercury for four or five days after the cessation of medication. In their last series of experiments, rabbits received the drug, and were killed at different intervals: in half an hour the metal could be found in all the tissues, the liver and kidneys containing most of it; in four days, or even in a shorter time, mercury given in a single dose was all eliminated, and could not be found in the tissues.\*

The evidence in favor of the storing up of mercury in the system is overwhelming. In 1880 Vajda and Paschkis stated that they found the metal in the urine in different cases, six months, one year, two years, and even twelve and thirteen years after the mercurial course. Mayençon and Bergeret found that the exhibition of potassium iodide forty-eight hours after the cessation of a mercurial course, when the urine was free from mercury, would bring about the immediate elimination of mercury. Apparently, using all precaution and having the patient carefully watched, H. Stein has obtained weighable amounts of eliminated quicksilver from the urine four weeks after its inunction. Schuster has found it in the feces three months after the cessation of a mercurial course; indeed, he believes that it is thrown off more freely and constantly by the intestines than by the kidneys. He also asserts that elimination is completed six months after the cessation of an ordinary mercurial course. According to Gola when the kidney elimination is great the intestinal output is small and *vice versa*. In an elaborate memoir on the elimination of mercury, Balzer and Klumpke state that extraordinary exacerbations and remissions occur in the elimination during treatment, that Michaelowsky and Souchow have shown that the effect of potassium iodide is small, but that Stepanow has proved that the hot-air baths increase enormously the elimination. It appears to be established by Stein, that in these cases of long continuance the mercury escapes not only through the kidneys, but is also excreted by the salivary glands as well as by the intestines, and hence its continuing elimination may be overlooked by the chemist, who simply studies the urine.

**Physiological Action.**—After absorption, all of the preparations of mercury appear to affect the system very similarly. When a mild, unirritating, preparation is introduced into the system so as to produce constitutional effects, the first symptoms of its action are to be looked for in the mouth. In the mildest degree these symptoms consist of a slight fetor of the breath, and some soreness of the teeth when knocked forcibly together or struck with a key. Mercurial fetor of the breath is generally the first indication that the drug is affecting the system, and is sooner or later accompanied by a disagreeable metallic taste. If the use of the mercury be persisted in the gums

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\* *Method of Preparing Tissues for Microscopic Detection of Mercury.*—J. Almkvist (*S. J.*, Bd. cclxxx., p. 177) soaks the freshly cut pieces for eight or ten hours in a solution of sulphuretted hydrogen, containing four per cent. of nitric acid, producing a yellow precipitate of mercuric sulphide; subsequently he hardens in alcohol or other fluid not containing iodine, and cuts.

become swollen, soft, and spongy, bleeding on very slight abrasion, and there is a decided increase in the secretion of saliva. Beyond this point the therapist is never justified in carrying the use of the drug. If it be done, the local symptoms in the mouth increase in severity, the tumefied gums become inflamed, very vascular, and marked by a dark red line at the junction of the teeth; the tongue is also swollen, sometimes enormously, protruding from the mouth, whose closure it may entirely prevent; the teeth are loosened in their sockets; the saliva is enormously increased in quantity and altered in quality, forming great, ropy, viscid masses, which pour over the thickened lips; the parotid glands, and even the submaxillary, are very much enlarged and tender. Severe ptyalism may be accompanied by marked fever, and nephritis is a not uncommon occurrence. Loss of the teeth, extensive ulceration of the soft parts, and even necrosis of the jaw-bones have occurred, and death from exhaustion resulted, or the patient struggled through to recovery, seamed and disfigured for life. In these cases passive hemorrhages often recur again and again, and may contribute largely to a fatal result. During severe ptyalism emaciation goes on rapidly, and seems to especially affect imperfectly organized tissues, so that exudations very generally rapidly disappear. The disturbance of nutrition is further shown in some cases by the occurrence of ulcers upon the extremities. The blood suffers very decidedly, becoming more fluid and watery than normal and having its power of coagulation impaired. According to the researches of Wright, its solid constituents are notably diminished, including albumin, fibrin, and the red corpuscles, and it contains a large quantity of fetid, fatty material. These observations of Wright have been confirmed upon animals by Wilbouchewitch, and by I. Hughes Bennett.

Although large doses of mercury lower the general nutrition and destroy the crisis of the blood, it is probable that when given in very minute doses it has tonic properties.

In 1869 Liégeois asserted that the subcutaneous injection of very minute doses of quicksilver produces in healthy men an increase of their bodily weight, and in 1876, in two experiments, E. L. Keyes found that not only was the bodily weight increased, but, as determined by actual count, the number of the red corpuscles was decidedly augmented. Hermann Schlesinger has laboriously experimented upon rabbits and dogs. All other conditions being similar, those rabbits which received the mercury increased in weight a little more than did those to which mercury was not given, but the augmentation of the red blood-disks was distinctly greater in the mercurialized animals. With dogs the results were more decided, both bodily weight and blood-corpuscles increasing much faster in the animals to which mercury was given. I. Hughes Bennett had previously obtained results similar to those quoted, and Schlesinger thinks that it must be considered proved that very minute continuous doses of mercurials tend in the normal animal or man to increase distinctly the weight of the body and the richness of the blood, but that it is scarcely proper to call them tonic, as in his belief they act by hindering oxidation and restricting waste, and not by aiding in reconstruction,—a conclusion which is purely theoretic and unproved. In some cases of syphilitic anemia the effect of mercury in increasing the number of red blood-corpuscles is very marked.

This effect is, however, to be attributed to the antisyphilitic influence of the remedy rather than to any specific action on the blood-making organs. (For elaborate paper, see L. Gaillard.)

The ordinary symptoms of mercurialization have been sufficiently described, but there are on record various anomalous cases. In some instances the chief symptoms of mercurialism have been cutaneous.

The usual eruption is a polymorphic erythema, resembling more or less that of scarlet fever. In rarer cases the eruption may be distinctly erysipelatous, with subdermal œdematous swelling. Sometimes it takes the form of urticaria, or even of a roseola; a very severe eczema, becoming finally pustular, has in some cases been produced, most frequently as the result of an inunction; while mercurial pemphigus and purpura have both been recorded. Usually the eruption is fugacious, being followed in two or three days by more or less desquamation, but very grave cases have been recorded in which there has been a universal dermatitis, with great swelling of the face and extremities, excessive desquamation, followed by thickening and infiltration of the subdermal tissues, excoriation, violent fever, disturbance of the respiration, and death; or, if the patient survive, months of illness (see M. A. Morel-Lavallée).

Sometimes the influence of mercury falls almost exclusively upon the nervous system, and produces a peculiar train of paralytic phenomena.

Nervous mercurialism occurs chiefly when mercurial vapors find entrance through the lungs, and is most frequently seen in workers in the metal. It is generally the result of long exposure; but that it may be produced in a very short time is proved by the case, related by Christison, of two barometer-makers who slept one night in a room containing a pot of mercury upon a stove. One was severely salivated, the other was affected with a shaking palsy which lasted all his life. According to Sigmond, the attack of mercurial palsy, which is sometimes sudden, sometimes gradual, begins with unsteadiness and shaking of the extremities and of the muscles of the face, which movements interfere with walking, speaking, or chewing; the tremors become frequent, nay, almost constant; "every action is performed by starts." If the exposure be continued, sleeplessness, loss of memory, and death terminate the scene. A peculiar brownish hue of the whole body, and dry skin, generally accompany the disease. In its first attack it may be mistaken for St. Vitus's dance; in its latter stages, for delirium tremens. According to Noël Guéneau de Mussy, these two forms are distinct varieties rather than different stages of mercurial tremors. In the latter the affection simulates *paralysis agitans* in its shaking movements; in the former the motions are violent, and occur independently of the will of the patient, even when he is lying quietly in bed. In a case reported by L. Langer, the electro-contractility of the affected muscles was much heightened.

Paralysis from chronic mercurial-poisoning is said to be not a rare affection among artisans and miners who are in their daily occupation exposed to contact with the metal or its fumes. The subject has been thoroughly discussed by M. M. Letulle, to whose paper the reader is referred for a collection of recorded cases and for details. In a case reported by Sigmond, symptoms similar to those of chronic lead-poisoning, including wrist-drop, followed repeated mercurial inunctions. In some cases mercurial paralysis takes the form of multiple palsy, or of a brachial or crural monoplegia, or of an obscure local palsy, as in a case reported by Küssmaul, in which there was aphonia from paralysis of the laryngeal muscles. Almost invariably the loss of motor power is accompanied by an anesthesia, which may be wide-spread or may be in isolated islets, or may take the form of hemi-anesthesia. The loss of sensation is very rarely absolute; simple loss of the thermic sensibility or analgesia may exist alone. Partial anosmia or amblyopia may show that the nerves of special sensation are affected. Neuralgic pains may be the permanent result of a mercurial exposure, and epilepsy and even insanity, most fre-



quently of the melancholic type, are stated to have been so produced. According to Letulle, trophic changes are not common, the paralyzed muscles not undergoing atrophy, and retaining their normal relations to the galvanic and faradic currents. When the thighs are affected the knee-jerk may entirely disappear. Guinon describes violent hysteria following upon chronic mercurial-intoxication.

In some cases exposure to the vapor of mercury, or even its persistent medicinal use, has resulted in the production of a state of the system somewhat resembling scurvy, characterized by great anemia, emaciation, and general loss of power, with loss of the hair, aching pains in the bones and joints, œdema, fetid breath, diarrhœa, and generally disordered secretions. This is the so-called *mercurial cachexia*.\*

There is some reason for believing that the pancreas is especially affected by mercury. Thus, in a case related by Copland, a woman after excessive salivation experienced deep-seated epigastric pain and heat, with nausea, thirst, and fever, and voided thin stools containing liquid resembling salivary fluid. At the postmortem the pancreas was found weighing four ounces, red, congested, and with its duct dilated.

The experiments of I. Brauer and of V. Tirelli show that in the lower animals very large doses of mercurials have a powerful depressing influence upon the central nervous system, and may produce death by respiratory paralysis; that when smaller doses are given a condition of nervous excitement is produced, with increase of the tendon-reflexes, followed by partial paralysis and ataxia; and that in chronic poisoning by very small doses continuously administered a degeneration of the nervous system takes place, probably beginning in the anterior motor cells of the spinal cord. This degeneration appears, however, not to be characteristic of the mercurial poisoning, but to be similar to that produced by phosphorus, arsenic, and various other poisons.

Little attention has been paid to *local mercurial* poisoning, but A. W. Foot has reported the production of paralysis of the muscles of the hand and forearm by contact with the red mercury iodide during the rubbing of cattle with a salve containing it. It is asserted that in some peculiar persons the external, and even the internal, use of small amounts of mercurials will produce violent eczema or other skin-eruptions (Alexander).

The constitutional action of mercury shows that it has relations to the nutrition of the whole body. The alterations in the blood, the wasting, the perverted functions of nerves and of glandular tissues, the various skin eruptions, all point to a profound influence upon the whole organism. After death from such irritant preparations of mercury as corrosive sublimate, violent diphtheritic colitis is the ordinary lesion, and, as was first shown by Salkowsky, structural alterations abound in the kidneys, accompanied by a peculiar deposit of calcium phosphate: that the renal lesions may be produced by the non-irritant preparations of mercury has been shown by B. Silva,

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\* For an interesting paper in regard to mercurialism in looking-glass makers, see article by Wollner (*Munch. Med. Wochen.*, July, 1892).

who has found true desquamative nephritis in dogs to which calomel had been given. Felix Klemperer discusses the literature of the subject fully, and concludes that the successive changes in the kidneys are: excessive hyperemia, parenchymatous nephritis, hemorrhagic nephritis, with wide-spread degeneration of the epithelium, and in about one-half of the cases deposits of chalky material. Virchow states that the coexistence of distinct renal chalky deposits with diphtheritic hemorrhagic colitis justifies the diagnosis of corrosive sublimate poisoning, but Klemperer affirms that this condition can be produced by bismuth and some other poisons. The later researches of E. Lentert led to a similar conclusion,—namely, that the calcification of the kidneys makes the diagnosis of corrosive sublimate poisoning very probable but not assured. The calcification of the kidneys, which is often accompanied by true calcareous deposit in the tubules, and which may be sufficient to cause the kidney structure to cry out under the scalpel, was attributed by Prevost to the decalcification of the bones; a theory which seems to have been disproved by Klemperer (confirmed by Paul Binet).

According to our present evidence, it does not seem probable that mercury increases the nitrogenous waste. It is true that Hermann von Boeck, in a case of mercurialization in a man, found that there was a very slight increase in the elimination of nitrogen during the mercurial periods, but H. Schröder, and Guttenberg and A. Gurber, in experiments made upon rabbits, obtained an absolute decrease in nitrogenous elimination during mercurial poisonings.

**Therapeutics.**—The use of mercury in affections of the liver and of the alimentary canal is fully discussed in another portion of this treatise; and, although the drug has been used for almost innumerable purposes in times past, it seems here only necessary to speak of its action as an antiphlogistic and as an antisypilitic.

*Antiphlogistic Action.*—The use of mercury in inflammation originated towards the close of the eighteenth century with Robert Hamilton, and soon became universal in England and America. It is a matter of regret that no sufficient analyses of the blood of pyralized persons have been made to determine exactly what are the changes produced in the vital fluid by mercury. The indications are, however, very strong that chief among them is a lessening of the amount of fibrin. As is well known, increase of the hemic fibrin is one of the most characteristic effects of inflammation: consequently, theory, instead of being opposed to the antiphlogistic use of calomel, affords at least some grounds for the belief that there is more or less antagonism between the processes of mercurialization and of inflammation.

All important evidence as to the antiphlogistic value of mercurials at present available is clinical, and even of this it seems impossible to find much that is very exact and of such nature as to exclude possible fallacies. It is the enormous mass of testimony that overrides the probability of fallacy. It is the general judgment of the profession, founded upon the thousand daily observed bedside facts,

that endorses the use of mercury as an antiphlogistic. In other words, our knowledge of the value of mercurials in inflammation at present is clinical rather than experimental, empirical rather than scientific, but it seems scarcely possible that it is not correct. There is one inflammatory affection—*iritis*—which, from its anatomical relations, is completely visible at all stages; and the effects of the drug upon its processes have been noted from day to day hundreds of times. Oculists are, we believe, agreed that when there is a marked tendency towards the exudation of lymph in this disease, mercury should be exhibited until *ptyalism* is induced.

Of all inflammations, those of the *serous membranes* seem to be most allied to *iritis*; and it is exactly in the condition above spoken of, where there is a tendency to fibrinous exudations in *pleuritis*, *peritonitis*, and *pericarditis*, that mercury is so constantly employed with so good an effect. In parenchymatous inflammations, especially in *pneumonia* and in *hepatitis*, mercury has been used with asserted advantage by many practitioners, but its value is certainly more questionable than in serous inflammations. In *pseudo-membranous angina* or *laryngitis*, and in true *diphtheria*, the mercurials are very useful remedies; they should be given in small repeated doses, preferably in the form of dry calomel powders, it being probable that the good effect is at least in part due to the diffusion of the mercurial over the diseased surface and the consequent antiseptic influence. There is much doubt as to the exact advantageousness of mercurials in *endocarditis*; but, as it is extremely important, if possible, in that disease, to prevent exudation, and as mercury is the most efficient known agent for effecting this, it should be administered freely and at once.

In whatever disease a mercurial is administered as an antiphlogistic, it should be given during the stage of exudation, and to facilitate the absorption of the newly organized lymph after it has ceased to be thrown out. In the majority of cases mercury given for its constitutional effects should be combined with opium, to prevent its acting on the bowels.

Calomel should not be used in *adynamic inflammations*, or where the exudation is serous rather than fibrinous. In *puerperal peritonitis* it has been strongly advocated by some and as strongly condemned by others, simply because there are two varieties of the disease, the *sporadic* or *sthenic*, and the *epidemic* or *asthenic*; and in the one both bleeding and calomel are strongly indicated, while in the other they are effective only for evil.

*Mercury as an Antisyphilitic.*—The literature concerning the use of mercury in the treatment of syphilis is so enormous as almost to defy analysis; through the discussion, however, has finally been reached practical unanimity of professional opinion, the only points of difference being as to details of “how” and “when” the mercury should be employed.

Whenever a venereal ulcer offers the characteristics of a true chancre, mercury should be exhibited. Many practitioners believe



that it is wiser for diagnostic purposes, in all cases of doubt as to the character of the primary sore, to withhold the mercury until secondary manifestations appear. Under any circumstances, so soon as the diagnosis of syphilis is clearly established, mercury should be employed in some form or other. Our own practice is in the beginning of the treatment to push the mercury to the point of mild ptyalism,—*i.e.*, to the production of slight evidences of constitutional drug action,—and then to continue the medicine persistently in small doses for at least eighteen months, increasing the dose up to mild ptyalism if at any time there should be a recrudescence of the symptoms.

In *tertiary* syphilis mercury is to be used cautiously. It is not, however, the mere length of time that has elapsed since the infection, but the condition of the patient, that guides the judicious practitioner. So long as there is no decided cachexia, if the patient has not recently been through a mercurial course, mercury should be freely used when the local lesion threatens to kill directly or to produce organic changes in a vital organ. Thus, a gumma in the heart-wall, in the upper spinal cord, or in some vital brain-region may imperatively demand active mercurialization. We have twice seen a patient slowly recovering from brain-syphilis under the influence of the iodides die by the accident of an epileptic arrest of respiration. In these cases the more rapid resolution of the gummatous masses by mercury, had that drug been exhibited, would in all probability have prevented the fatal fit. In *hereditary* syphilis a prompt mercurial impression offers the best chance of relief. At any stage of syphilis some caution and judgment should be used in the administration of mercury. As was shown by Keyes, the small dose of mercury in infected patients frequently acts distinctly in increasing the number of red blood-disks. Wilbouchewitch found that the mercurial when first exhibited increased the number of red blood-corpuscles in syphilitic patients, but after a time appeared to produce anemia. Whatever preparation be employed it should be so administered as to cause only signs of the constitutional action in the mouth. It is never necessary to ptyalize the patient severely. There are various methods by which this may be done. That most frequently employed, because most convenient, is the administration of small doses of calomel or blue pill by the mouth: from one-fourth to one-half grain of calomel, or twice as much of the blue mass, combined, if necessary, with opium, to prevent its action upon the bowels, may be given three times a day, and increased if required. Instead of the internal use of the mercurial, the system may be brought under its influence by inunctions.

In practising inunctions it is essential to remember that when mercury is applied to a hairy surface it is very prone to cause a troublesome irritation, due to inflammation about the hair-follicles. Indeed, the continuous application of the mercurial to almost any surface of the body will cause finally an eczematous eruption. Further, when the skin is in thoroughly good condition it absorbs much better than when it is irritated. The frequent use of the hot baths seems also

to aid in the absorption, and possibly also in the elimination of the mercury; and the good effects obtained at the Arkansas and other thermal springs largely depend upon the frequent employment of the hot bath with the free use of the mercurial. It is therefore usually better to have the inunction practised in the evening, after the patient has had a prolonged bath; and in cases of great urgency the baths may be repeated two or three times a day, so as to produce free sweating, and the inunction practised, it may be, twice a day. In order to avoid irritation of the skin, a regular order should be maintained in the application, as follows: *first day*, inner side of both upper arms; *second day*, inner side of both thighs; *third day*, inner side of both forearms; *fourth day*, inner side of both legs; *fifth day*, upon both groins; *sixth day*, upon the back; *seventh day*, recommence the series.

The advantage of inunction is that the digestion is less likely to be disturbed than when the drug is exhibited by the mouth;\* the disadvantages are the greater or less publicity which it entails, the trouble which it involves, and its apparent dirtiness. In private practice it is rarely practised except in the case of infants, when the mercurial ointment is rubbed into the abdomen and armpits, or often simply smeared upon the flannel roller or binder which usually envelops the body. The mercurialization of the nurse, with the object of affecting the child, is unjustifiable, unless the nurse and the nursing are alike diseased: indeed, to allow a syphilitic child to feed at the breast of a healthy woman is a crime.

Mercury may be used hypodermically, often with great advantage, in the treatment of syphilis. The search after novelties by clinicians and chemists has led to the invention of very many new preparations and the production of a very large literature, which was summarized in previous editions of this work, and is discussed in great detail in current monographs on syphilis. As the result of much experience, however, we are confident that the whole matter can be summed up in a single sentence,—namely, that no mercurial preparation has any distinct advantage over corrosive sublimate for hypodermic administration; and that the great mass of the proposed preparations, including all those which contain calomel, are much more dangerous than is the corrosive chloride. From one-sixteenth to one-eighth of a grain of the bichloride should be injected deeply into the muscles of the back or of the thigh daily or every other day, according to the needs of the case; care being exercised to see that the part is well rubbed immediately after the injection, so as to dispel the local accumulation of fluid, and that injections are not given on successive days in places near to one another. In some cases very pronounced

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\* The action of inunctions is usually very mild and tractable, but Von Sackur (*Berl. Klin. Wochenschr.*, 1892, xxix.) has reported a case of death in six days, preceded by symptoms of violent irritation of the stomach, the intestines, and the kidneys, with furious gangrenous pytalism, apparently produced by a single inunction with mercurial ointment. Ludwig, of Vienna, in an examination to determine the distribution of mercury given by inunction, found that it was most abundant in the kidneys, liver, and spleen; then in the alimentary canal (least in the stomach and most in the large intestine). In the muscles the amounts were variable, in the cerebrum never sufficient to be weighed (*Internat. Klinisch. Rundschau*, 1892, vi.).

pain is produced; this can be overcome, however, by injecting one-quarter of a grain of cocaine immediately before the injection of the mercurial into the same spot. The advantages of hypodermic medication are the rapidity and power of influence, the cleanliness, and the avoidance of gastro-intestinal irritation.

Mercury is sometimes administered in secondary syphilis in the form of fumigations. The patient is placed upon a chair, and surrounded by a large blanket or, better, india-rubber cloth, so arranged as to fit tightly around his neck above, and below to encompass the chair. The mercurial preparation is placed upon a metal plate, heated by a spirit-lamp, beneath the chair, and the fumes are allowed to fill the space around the patient inside of the blanket. The heat produced generally causes the patient to sweat profusely, and in from fifteen minutes to half an hour the lamp should be withdrawn and the patient allowed to cool off, and after a time be put to bed and wrapped up in blankets, with the deposit of mercury still adhering to the skin. The fumigation may be practised every other night, or at longer intervals, and is believed by some to be especially useful in cases of secondary skin eruptions. Calomel, black oxide, and cinnabar are the preparations generally used; care must be exercised that the patient do not breathe the fumes.

In advanced secondary and tertiary syphilis the mercurial iodides, given by the mouth, are often very useful, but the combination of the corrosive sublimate and the potassium iodide is in many cases still more efficient. Usually not more than one-twelfth of a grain of the bichloride should be exhibited, three times a day.

It appears to be established that certain disagreeable and, perchance, serious effects may be produced by mercurials when freely and continuously used in the treatment of syphilis, against which the practitioner must be on his guard. The most important of these is nephritis, with its consequent albuminuria. According to Heller, the safest method of mercurialization, so far as the kidneys are concerned, is by the hypodermic employment of corrosive sublimate; the most dangerous, probably, being the use of inunctions. A very rare complication which has been attributed to the mercury is polyneuritis, which has especially been noted after free use of mercurial inunctions.\*

**Administration.**—For oral administration, when the constitutional effect is desired, either of the chlorides or of the iodides may be employed. For hypodermic use the corrosive chloride is probably the best preparation (see p. 369).

Mercury with chalk is much used as an intestinal antiseptic in inflammatory conditions of the bowel.

The mercuric oxides are used upon *ulcers*, *chancres*, etc., for their local effects, and are stimulant and alterative when diluted, mildly escharotic when in powder.† From yellow oxide is made the *oleate*.

\* See Leyden (*Deutsch. Med. Wochen.*, 1893, xix.) and R. von Engel (*Prager Med. Wochen.*, 1894, xix.).

† For severe poisoning by yellow oxide, see *Brit. Med. Journ.*, Sept. 1889.



The ointments of the oxides, also the ointment of the nitrate sometimes known as *Citrine Ointment* very generally require dilution with lard, and are much used in chronic *skin affections*, in obstinate *conjunctivitis*, in *psorophthalmia*, etc.

*Turpeth Mineral*, or *Yellow Mercuric Subsulphate*, which was formerly official—a lemon-yellow powder, sparingly soluble in water—is a compound of uncertain composition, which was at one time used as an emetic in *croup*. It is, however, a very dangerous remedy, since, if it fail to vomit, it may cause a fatal gastro-enteritis, especially in the young child. Two cases of such character are recorded by A. McPhedran. Forty grains have caused death in the adult; profuse salivation came on in six hours. Dose as an alterative, one-fourth to one-half grain (0.016–0.032 Gm.); as an emetic, for a child two years old, two grains (0.13 Gm.), repeated in fifteen minutes, if necessary.

*Black Wash* and *Yellow Wash*, two non-official but favorite preparations, are respectively made by the addition of a drachm of calomel to a pint of lime-water, and of half a drachm of corrosive sublimate to a pint of lime-water. They depend for their virtues upon the black and yellow oxides of mercury, and are used exclusively as local applications to *chancres* and other *syphilitic ulcers*. The yellow wash is much the more stimulating of the two.

*Solution of Arsenous and Mercuric Iodides* contains one per cent. each of the arsenous iodide and the red mercury iodide. It was originally suggested by a surgeon of Dublin, by whose name it is very generally known. *Donovan's Solution* is a powerful alterative, used chiefly in very obstinate chronic scaly *skin diseases*, when the local action is of a very low grade, and in *chronic rheumatism*. It is an exceedingly active preparation, very capable of acting as a corrosive poison, and when administered a little too freely is said sometimes to cause salivation. When applied locally, it acts as a violent irritant.

**Toxicology.**—The bichloride of mercury (corrosive sublimate) and the biniodide (red mercuric iodide) are each so intensely irritant in their local action that they may give rise to acute poisoning which frequently proves fatal. On account of its wide use as a disinfectant, corrosive-sublimate poisoning is by no means rare. The symptoms are those of irritation of the alimentary tract and in severity are proportionate to the dose.

If the latter be small, the manifestations may be only some nausea, slight burning in the stomach, colicky pains in the abdomen, and diarrhœa. After large doses these symptoms are intensified. The subject first experiences a peculiar metallic, coppery taste at or shortly after swallowing the poison. If the solution be concentrated, deglutition is interfered with by a spasm of the muscles of the throat and larynx, causing a feeling of suffocation, and sometimes even the rejection of the draught. Then burning pains are experienced in the œsophagus and stomach, followed by violent vomiting, at first mucous, then bilious, and finally bloody, and by severe abdominal pain and tenderness, with profuse purging, at first serous in character, but

afterwards affording only small, mucous, bloody stools, which are often voided with much straining. The breath generally becomes fetid and offensive in a very short time. In the course of two or three hours, very rarely in less than an hour, collapse occurs, with small, frequent, irregular pulse, pinched, anxious face, cold extremities, and finally death, preceded, it may be, by fainting, convulsions, and coma. The urine is very much lessened in quantity, is sometimes albuminous, or even bloody, and not rarely is suppressed. If the patient survive several days, a petechial eruption may appear, and salivation sometimes, but not always, occurs. In some cases, after the collapse there is an attempt at a febrile reaction, which soon, however, gives place to a second and fatal prostration. When recovery occurs after severe poisoning, the convalescence is slow and protracted.

In the *treatment* of corrosive sublimate poisoning the most available antidote is some form of albumin, as white of egg, hashed meat or milk. After this opium and tannic acid should be used to quiet the vomiting and purging, and stimulants given as required. Demulcent drinks for the soothing of the gastric inflammation, and general sustaining treatment will be required during the long and difficult convalescence.

In regard to chronic poisoning with corrosive sublimate, sufficient has been said under the general heading, except that colicky pains and abdominal disturbance are more apt to occur with it than with the less irritating preparations. Hemorrhagic nephritis has been noted in a number of cases (H. C. Wood, Jr.). Arnozan asserts that chronic catarrh of the excretory ducts of the pancreas is a pronounced lesion in chronic poisoning of animals. It should be looked for in man, and its presence might be of medico-legal value.

Severe purging, and even fatal poisoning, may result from a single external application of this preparation of mercury,\* and in animals killed by hypodermic injections of it (see experiments of J. Rosenbach), diarrhœa and other indications of gastro-intestinal irritation are prominent symptoms,—facts which indicate that the bichlor de is eliminated unchanged from the alimentary canal.

### GOLD AND SODIUM CHLORIDE.

This salt of gold (Auri et Sodii Chloridum), which may be obtained in large, golden-yellow, prismatic crystals, is, according to the requirements of the U. S. Pharmacopœia, a slightly deliquescent powder, odorless, but having a saline and metallic taste. It is freely soluble in water.

**Physiological Action.**—The precise action of the preparations of gold upon the animal organism is not understood, but it is probable

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\* See case reported by Meeres (*Lancet*, Sept. 16, 1871), in which a solution (two grains to one fluidrachm) was applied with a camel's-hair brush to the head of a child nine years old, for the cure of tinea tonsurans. The symptoms were diarrhœa, profuse salivation, and great prostration, ending in death. Washing out the vagina with a solution of corrosive sublimate, has caused severe and even fatal poisoning. (See H. C. Wood, Jr.) Marx and Sorge found that in pregnant animals acute corrosive-sublimate poisoning causes injury not only to the placenta but also to the fetal kidney.

that the soluble preparations are mostly irritant poisons, while the insoluble preparations are either not poisonous or else act slowly upon the general system. It is stated that gold and sodium chloride, in overdose, produces pain, inflammation, and even ulceration of the stomach and bowels, and otherwise acts as a corrosive poison. It is affirmed that the gold preparations, in moderate doses, cause increased fulness and frequency of the pulse, and augment the urine and insensible perspiration, without interfering with the appetite or the regular action of the bowels; but that, if the dose be pushed too far, general irritation is apt to be produced, and inflammation to seize upon some organ, according to the predisposition of the individual, and fever is developed.

**Therapeutics.**—Although gold and sodium chloride has been largely used in the treatment of *neurasthenia*, *hysteria* and similar nervous conditions, there is no good evidence that it possesses any therapeutic value in these conditions. It appears to have been introduced in medicine from the idea that it formed part of the famous Keeley cure for the alcohol habit. According to the sworn statement of one of the founders of the Keeley Institute,\* the Keeley treatment contains no gold in any form.

The gold and sodium chloride has been commended by various practitioners in *scrofula*, advanced *syphilis*, *chronic rheumatism*, and *chronic diseases of the joints*. Charles G. Stockton asserts that it has a special influence upon the lithemic and fatty degenerations which are prone to occur in advanced middle life. The salt is also employed with alleged excellent results in the various *spinal and cerebral sclerosis*.

**Administration.**—The gold and sodium chloride may be given in solution or in pill, in doses of one-twelfth of a grain, increased to one-sixth or even one-fourth (0.01–0.016 Gm.) three times a day. It may also be administered hypodermically, producing some pain, but usually no serious or permanent local irritation. In many cases in which it has been used the moral effect of the hypodermic injection has probably been greater than the direct influence of the remedy.

**INSOLUBLE GOLD PREPARATIONS.**—The *oxide*, *iodide*, and other insoluble preparations of gold have been recommended as alteratives in *scrofula*, *skin diseases*, and *secondary syphilis* of various forms, in doses of from one-fifteenth to one-tenth of a grain, three times a day.

### IODINE.

Iodine is recognized by the U. S. Pharmacopœia both in the form of metallic iodine and in the form of hydriodic acid and many of its salts. It is a soft, friable, opaque substance, occurring in crystalline scales with a semi-metallic lustre and of a bluish-black color. Its odor resembles that of chlorine; its taste is hot and acrid. It is somewhat volatile at ordinary temperatures, but when heated to 237.2° F. melts and emits the beautiful purple or violet vapor to which it owes

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\* See report in *J. A. M. A.*, 1907, xlix. p. 1861.



its name. It is freely soluble in glycerin, alcohol, and ether, but requires five thousand times its weight of water to dissolve it. With starch it strikes a deep blue color, and this test is so delicate that it will indicate the presence of iodine in four hundred and fifty thousand times its weight of water. In testing animal liquids, such as urine, for iodine, a small quantity of nitric acid should be added to insure its being free in the liquid.

Absolute *hydriodic acid* is a gaseous substance, a ten-per-cent. solution of which is recognized by the U. S. Pharmacopœia under the name of diluted hydriodic acid. This is a clear, colorless fluid, with an acidulous taste. The iodides of sodium, potassium, strontium, ammonium are all official. They are all white crystalline salts, freely soluble in water and having a salty, somewhat bitter taste. They are all more or less deliquescent.

Iodine and the iodides form insoluble compounds with most of the alkaloids, with the salts of silver, lead and mercury.

#### Official Preparations :

Iodum.....	Not used internally.
Tinctura Iodi (7 per cent.).....	External use only.
Liquor Iodi Compositus [Lugol's Solution]	
(Iodine 5 per cent.; potassium iodide	
10 per cent.).....	5 to 10 minims (0.3-0.6 C.c.).
Unguentum Iodi (4 per cent.).....	External use.
Acidum Hydriodicum Dilutum (10 per cent.).....	15 to 20 minims (1-1.3 C.c.).
Syrupus Acidi Hydriodici (1 per cent.).....	1 to 2 fluidrachms (4-8 C.c.).
Ammonii Iodidum.....	3 to 20 grains (0.2-1.3 Gm.).
Potassii Iodidum.....	3 to 20 grains (0.2-1.3 Gm.).
Sodii Iodidum.....	3 to 20 grains (0.2-1.3 Gm.).
Strontii Iodidum.....	3 to 20 grains (0.2-1.3 Gm.).
Unguentum Potassii Iodidi (10 per cent.)....	External use only.

**Physiological Action.**—*Local Action.*—Metallic iodine, when applied to any part of the body, acts as a very powerful irritant, or, if in highly concentrated form, as a mild caustic. The tincture stains the skin yellow, and causes, if applied with sufficient freedom, smarting, some erythematous inflammation, and finally desquamation. Its repeated application blisters and destroys the cuticle. Upon mucous membranes its action is more intense than upon the skin.

The iodides are absorbed rapidly and circulate chiefly as an iodide, according to Lasser, escaping unchanged. Metallic iodine appears to unite, to a large extent, with the alkalies of the tissue and to be eliminated chiefly in the form of an iodide, but also partly in organic combination (E. Harnack). The elimination is usually prompt and chiefly through the kidneys, although iodine has been recognized in practically all the tissues and fluids of the body, even in serous exudates (Leuch).

Anten finds that absorption of potassium iodide is retarded by the presence of mucilaginous substances and hastened by potassium nitrate or sodium chloride and that the elimination of a single dose is complete in about forty hours, seventy-five per cent. escaping through the kidneys. Iodine has also been recognized in

the secretions of the skin by Taylor and according to Seé may exist in saliva even after it has disappeared in the urine. According to these authors the elimination is sometimes irregular so that the drug may accumulate in the system, but, in a patient under our care, taking daily 360 grains of potassium iodide, John Marshall recovered daily 265 grains in the urine. (See also Ehlers.) According to Kämmer and Binz the iodides are partially decomposed in the tissues liberating free iodine.

Although the toxic action of iodine has been studied to some extent,\* we know very little concerning the action of therapeutic doses. It is frequently stated that the iodides have the effect of dilating the blood-vessels, but nearly all the scientific evidence on this point indicates that this belief is incorrect.

Sée and Lapicque believe that potassium iodide acts upon the heart like digitalis, but that it also dilates the vessels. On the other hand, Stockman and Charteris, and Prevost and Binet have found that, unless given in enormous doses, potassium iodide has no effect upon the circulation and Rose has found evidence of vascular spasm.

Von Zeissl asserted that the injection of the solution of iodine in sodium iodide into the jugular vein produces a temporary increase of pressure in the left auricle, with elevation of the pressure in the pulmonary arteries and pulmonic oedema, the latter phenomenon being due to narrowing of the vessels by a direct influence of the iodine upon their walls. He further affirms that the injection of the iodine-iodide solution into the distal end of the carotid causes an increase of the general blood pressure, but a much greater increase of the intra-cerebral pressure, the result of an oedematous exudation.

*Action on Kidneys, and Excretion.*—During its passage through the kidneys iodine undoubtedly exerts an influence upon those organs, as is shown by its producing albuminuria at times. It is indeed asserted that it occasionally causes a true tubular nephritis. The evidence as to its effect upon the solids of the urine is both contradictory and insufficient.

Hermann von Boeck found that the ingestion of iodine does not increase notably the elimination by the kidneys or bowels. On the other hand, M. Bouchard (quoted by Seé) declares on his personal experience that iodine does increase the daily elimination of urea, especially in diabetic patients. C. Handfield Jones analyzed the urine of six patients taking large doses of potassium iodide, and found in three cases diminished and in three cases increased output of nitrogen; the other elements of the urine also failed to show any distinct action of the drug. Eugene I. Duchesne found that potassium iodide and tincture of iodine notably increased the elimination of urea, while sodium iodide was followed by a distinct decrease of this excretion. All the preparations of iodine used increased the elimination of uric acid. Henrijean and Corin find that almost all of the iodides markedly increase the elimination of nitrogen as well as of the phosphates and chlorides. On the other hand, A. Haig affirms that the iodides have a marked effect in lessening the elimination of uric acid and the urates, and as a result of this diminish the arterial tension. I. Wallace has found that the iodide lessens the elimination of lime salts through the kidneys; but his analyses were not sufficiently repeated to prove that this is a constant effect.

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\* For a research upon the physiological action of large amounts of potassium iodide injected into the blood, see *Arbeiten aus dem Pharmak. Laborator. zu Moskau*, i. 125. As it does not seem to throw light upon the therapeutic use of the drug, it is not here analyzed.

**Therapeutics.**—As an alterative, iodine is of especial value in *chronic scrofula*. In those cases in which there is indolent enlargement of the lymphatics, which exhibit no tendency, or but little tendency, to suppurate, it is of especial value. Except in very acute cases, however, it should always be tried, even when the glands do tend towards suppuration, especially as it exerts a very beneficial influence upon the ulcers left after suppuration. In other forms of scrofulous disease, in *chronic enlargements* of the *joints*, and *bone affections* of such nature, iodine is often of great service. As scrofulosis is generally, if not always, associated with lowered nutrition and with anemia, cod-liver oil and iron in some form should usually be administered as adjuvants. At the same time that the drug is exhibited internally in these cases, its ointment should be freely applied to the enlarged and indurated glands. Experience has demonstrated the value of iodine in true *goitre*. All tumors of the thyroid body are not goitre, however; cystic degeneration of it is very common, and is in no wise benefited by iodine. It is in simple hypertrophy of the gland that iodine used internally and applied externally over the tumor is beneficial. During the acute stage of enlargement the use of leeches is often of great benefit, and whenever much tenderness exists should precede the exhibition of the drug. In *phthisis* iodine sometimes does good, but only in the most chronic cases; and inhalations of its vapors, as have been recommended by Piorry, can be of service only by stimulating the bronchial mucous membrane and the surfaces of cavities. When softening is progressing and the lung breaking down, iodine appears to hasten the process.

In certain forms of *rheumatism* the iodides are of value. In the early, active stages of *inflammatory rheumatism* it is useless; but later, when the joint symptoms persist in a subacute form, the iodide comes very well into play. In *subacute* or *muscular rheumatism* the iodide is an efficient remedy. Often when the symptoms are very acute an iodide may advantageously be combined with the alkalies, and in lingering cases, especially where there is reason to suspect a gouty taint, with colchicum. In *sciatica*, in *lumbago*, and in *rheumatic neuralgia* following exposure to cold or wet, as in all other forms of subacute rheumatism, much is to be hoped for from its use. In *gout* the iodides are of less service than in rheumatism, but in the chronic form of the disease, and in the irregular, inherited gout which so frequently appears as neuralgia or other anomalous affection, they add to the efficiency of small continuous doses of colchicum. In *rheumatic gout*, or *rheumatoid arthritis*, they should be tried, although little is to be hoped for from their use. There is a good deal of clinical testimony as to the value of potassium iodide given continuously between the paroxysms of *asthma*. This disorder appears at times to bear a close relation to irregular gout or rheumatism, and it is probably under these circumstances that the remedy is efficient.

In *tertiary syphilis*, including in the term all cases of syphilitic bone, visceral, or nervous disease, iodine is really of inestimable value.



It must be given freely, and, when there is no cachexia, may be advantageously combined with the mercury bichloride. It is scarcely in place here to enumerate all the forms which tertiary syphilis may assume; but an iodide is useful wherever the dyscrasia has existed for a length of time.\* Recently potassium iodide has been largely employed in the treatment of *actinomycosis*, and seems to exercise in this disease a specific action.

Potassium iodide appears to have the power of promoting absorption of serous fluids, and certainly is of value in *chronic pleuritis* with effusion, in *chronic pericarditis*, and even in *chronic hydrocephalus*. In aortic *aneurism* large doses of potassium iodide with continuous rest in the horizontal position are much used, but its value is questionable.

In various chronic *metallic poisonings* the potassium iodide is of great service. With both lead and mercury it forms double salts, which are soluble, and there is very good reason for believing that the formation of these salts takes place in the economy, and that the metal which has been lying in an insoluble condition in the various tissues is taken up and excreted. Severe salivation and ulcerative stomatitis have sometimes resulted from the use of the potassium salt in those who had previously taken large quantities of mercury;† and in Melsen's experiments, dogs to which insoluble preparations of mercury had previously been given without the induction of severe symptoms afterwards died under the action of the iodide, the mercury also having appeared in their urine. The experiments of Mayençon and Bergeret (quoted in the article on Mercury) afford striking confirmation of these facts, and seem to render the evidence irresistible that the iodide does bring about the elimination of mercury. In regard to lead, the researches of Parkes, Melherbe, Sieveking,‡ and Marshall have shown that very frequently in cases of chronic lead-poisoning the exhibition of potassium iodide causes the appearance of lead in the urine. This chemical evidence is abundantly corroborated by clinical experience, so that in all cases of chronic metallic-poisoning the persistent use of potassium iodide should be tried.

*Local Application.*—As a simple counter-irritant, iodine is very frequently employed when it is desired to maintain a mild, persistent influence, as in *chronic rheumatic affections* and sometimes in *phthisis*. For this purpose the tincture is generally preferred, and it should be applied freely once or twice a day, or every other day, according to the susceptibility of the patient's skin. In various affections of the skin iodine has been employed with asserted advantage. In *erysipelas* of the skin very beneficial results have been ascribed to its local use, but great care is necessary lest it be applied too strong. We have seen very serious results from the destruction by it of the skin in this affection. If the full strength of the tincture be used, it should be

\* For complete literature on this subject, see Lieblein, *B. K. C.*, 1900, xxviii. 198.

† See Budd (*Brit. and For. Medico-Chir. Rev.*, xi, 202) for a striking case.

‡ See Stillé's *Therapeutics*, ii. 735, Blanchard & Lea, 1864.

applied at first very lightly, and not more than once in the twenty-four hours. In *psoriasis*, in *acne*, and in *parasitic skin diseases* it has been used, but holds only a second rank among remedies. In a similar manner it is employed in various chronic diseases of the mucous membranes, such as *ozena*, *leucorrhœa*, *chronic cystitis*, *chronic dysentery*, and *scrofulous ophthalmia*,—whenever, in a word, an alterative, stimulant action is desired. In cases of *retraction of the gums*, with consequent loosening of the teeth, Stillé recommends the application, with a camel's-hair brush, after each meal, of an aqueous solution (one grain to a fluidounce) of iodine, the mouth being immediately afterwards washed. The most important external use of iodine is as a resolvent in cases of indolent *glandular hypertrophic enlargement*, and where there are large watery exudations, as in some forms of *chronic pleurisy* and of *diseased joints*.

Iodine has been very largely employed by injection into serous cysts, as in *hydrocele*, for the purpose of exciting inflammation and causing obliteration of their cavity; but this use of it is purely surgical, and the reader is referred to treatises upon such subjects. In *chronic empyema* the injection of iodine after free exit has been given to the pus is often of the greatest service. The solution in the beginning should be very weak, containing not more than six grains each of iodine and of potassium iodide in a pint of water; with this the pleura should be daily washed out, the strength of the solution being gradually increased.

**Toxicology.**—Metallic iodine on account of its local irritant action is capable of giving rise to an acute form of poisoning.

A form of chronic intoxication, known as iodism, may be caused by the administration, over periods of time, of full doses of elementary iodine or the salts of hydriodic acid.

**Acute Poisoning.**—When taken internally, a single moderate dose of iodine causes merely some gastric uneasiness and a disagreeable metallic taste in the mouth; when larger amounts are ingested, the gastric uneasiness may be intensified into violent vomiting, with increased salivary flow, abdominal pains, and even purging. In sufficient quantity it is a poison, although very few deaths have been recorded as caused by it. The symptoms produced by toxic doses taken into the stomach are burning pain in the œsophagus and stomach, vomiting, purging, smallness of the pulse, general deadly pallor, lessening or arrest of the urinary secretion, sometimes violent excitement with convulsions, and collapse. Twenty grains of iodine are said to have caused death, and two drachms and a half have been recovered from.\* The vomit is yellowish brown or, if starchy matters have been present in the stomach, bluish. The injection of iodine into the cavities of the body for therapeutic use has several times been followed by cyanosis, thready pulse, repeated vomiting of matters containing iodine, excessive thirst, salivation, difficult urination,

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\* For cases, see Woodman and Tidy, also *Münchener Med. Wochenschr.*, Feb. 1887.

swelling of the eyelids, laryngeal pain, various eruptions upon the skin, high fever, and albuminuria. Sudden death may take place after some days from heart-failure.

E. Rose records a death following injection of iodine into an ovarian cyst. Very soon after it was given there ensued severe thirst, with great dryness of the throat and mouth, and then painless vomiting of watery matters containing iodine. The whole surface became very pale, the extremities cyanosed, the radial pulse very frequent, but so small that it could not be counted, the urine very scanty, dark brown, and rich in iodine. After a time reaction occurred. For three days the vomiting persisted, the pulse was very frequent, full and hard, and the cheek put on the glow of high fever, but the temperature did not rise above 37.18° C. On the fourth day exanthematous blotches, not disappearing on pressure, developed on the skin and in the mouth, the sputa became bloody, and menstruation occurred two and half weeks too soon. The urine remained scanty, and on the eighth day, when all other symptoms save swelling of the parotids had disappeared, still contained iodine, and was albuminous. On the tenth day, in the midst of apparent convalescence, the patient died suddenly. In a case reported by W. O. Culpeper two drachms of a tincture used externally on a child of eleven years destroyed all the skin from above the knees to below the ankles. After twenty-four hours there developed headache, backache, some diarrhoea, vomiting, great thirst, constant desire to urinate, suppression of urine, priapism, and giddiness; finally there ensued dysentery without rise of temperature, hiccough, hemorrhage from the bowels, and great giddiness ending in death on the sixth day.

In the experiments of Jörg and his pupils, doses of iodine of a grain to a grain and a half gave rise to colicky pains, increased appetite, watery stools, an increased secretion of urine, malaise, and some headache. When the dose was augmented to two grains, a diffused sense of heat and sexual excitement were superadded. Other observers have noted this abnormal sexual excitement, and some have stated that at times it is succeeded by atrophy of the mammæ or of the testicles. Stillé affirms that the menstrual flow may become excessive, or that during pregnancy abortion may be caused.

Very large quantities of iodine are asserted to have been taken without serious results. Julia de Fontenelle\* tells of a man who took two and a half drachms of iodine without experiencing any remarkable effects, and Magendie relates the case of a child four years old who swallowed ten grains without serious consequences.†

In the experiments of A. Höyges and Binz, preparations of iodine, potassium iodide, and iodoform in fatal doses produced in the lower animals wide-spread fatty degenerations.

*Iodism.*—Chronic iodic intoxication may manifest itself in several ways. The most common symptoms of iodism, as seen in the United States in non-goitrous individuals, are dull pain in the region of the frontal sinus, coryza, sore throat, ptyalism, and an eruption upon the skin, which is usually an acne, but may take almost any shape. In its serious forms it becomes pustular or bulla-like, and may be accompanied by much dermatitis, ulceration, and even very violent constitutional disturbances.

A remarkable iodic *dermatitis tuberosa* has been noted by Besnier, Duhring, and R. W. Taylor. In rare cases there is an excessive susceptibility to iodine, often

\* Quoted by Stillé (*Therapeutics*, ii. 731).

† For an elaborate, careful study of the action of large toxic doses of iodine upon the lower animals, see *Hoffman und Schwalbe's Jahresbericht*, 1879, 199.



accompanied by marked irregularity of the iodic symptoms. Thus, we have seen six grains of potassium iodide given in daily dose repeatedly provoke in a man violent conjunctivitis with œdema around the eye, beginning unilaterally, but involving the whole face in a violent erythema with great subdermal exudation. Iodic accidents are especially likely to be severe when there is kidney disease, as in a case reported by F. Wolf, in which forty grains of potassium iodide given in two days appear to have produced death. It is further possible that iodic accidents may depend upon gastric conditions, since Bjelogolowy believes that his researches have shown that when the contents of the stomach have a heightened acidity and contain the nitrites, iodine is set free in the stomach from the iodides and produces abnormal effects.

Rilliet (Trousseau's report on his memoir), who has had wide opportunities and has apparently studied the subject very closely, describes three forms of iodic intoxication: first, that in which the symptoms are those of gastric irritation; second, that characterized by nervous troubles, neuralgia, ringing in the ears, convulsive movements, disturbed intellection, with coryza, ophthalmia, salivation, vomiting, diarrhœa, polyuria, and cutaneous eruptions, and in some cases atrophy of the mammae in the female and of the testicles in the male;\* third, iodic cachexia, caused either by iodine or potassium iodide continuously used for many months. It is said to be most easily induced in goitrous persons, and is characterized by rapid emaciation, commencing mostly in the face, and severe nervous palpitations of the heart, with excessive appetite, which sometimes precedes and sometimes follows the loss of flesh. So long as the drug continues to be taken, these symptoms continue to progress, and after a time hysteria or hypochondriasis, with insomnia, manifests itself. The goitre, the mammae, and the testicles waste away together; but if the medicine be suspended and health gradually returns, while the abnormal growth reappears the sexual glands remain wasted. It is probable that some of the symptoms in these cases are due to principles taken into the blood from the wasting thyroid body. The second form of iodism of Rilliet, in which the nervous symptoms are prominent, has been spoken of by other authorities; and Brodie has especially noted disturbances of vision and paralysis. In some rare cases neuralgic pains and other disturbances of nerve-functions have occurred, indicating that iodine is capable of causing a peripheral neuritis.†

**IODIPIN.**—This is a yellow, oily fluid, said to be an iodine addition-product of sesame oil, containing ten per cent. of iodine in chemical combination. According to H. Winternitz, iodipin when taken internally passes unchanged into the intestines, where it is slowly digested with an absorption of iodine, probably as an alkaline iodide; and the final escape from the intestines of a portion of the iodipin unchanged. When it is injected hypodermically it forms a local depot, as it were, from which the iodine is very slowly, but continuously, absorbed. Under these circumstances it is said to produce no local disagreeable symptoms. Winternitz affirms that no absorption of iodine takes place after iodipin inunction or enemata. In chronic *syphilis* it has been used internally in doses of from fifteen to thirty grains (1–2 Gm.) of the ten-per-cent. iodipin, which may be injected daily, as recommended by Schuster. Naegeli recommends for the purpose of producing local absorption subconjunctival injections of one-third to one-half minim (0.02–0.3 C.c.) of iodipin in specific *retinitis*, *scleritis*, *keratitis dendritica*, and *keratitis neuromparalytica*. Dose of iodipin, one to two drachms, given in emulsion, three or four times a day.

### iodoform.

Iodoform, which was discovered by Serullas in 1822, and introduced into medicine by Glover in 1837, is a triiodomethane ( $\text{CHI}_3$ ), being therefore chemically related to chloroform and bromoform.

\* For a case of wasting of the testicles, see *Phila. Med. Times*, iv. 661.

† See *Therapeut. Monatshefte*, 1888, iii.

It occurs as a greenish-yellow powder of crystals, with a powerful and persistent odor, practically insoluble in water, sparingly soluble in alcohol but freely soluble in ether and in oils.

#### Official Preparations:

Iodoformum.....3 to 5 grains (0.2-0.3 Gm.).  
 Unguentum Iodoformi (10 per cent.).....External use only.

*Local Action.*—In itself iodoform is a non-irritant, slightly desiccant powder, which appears to be imbued with local anesthetic properties, so that the rectum may be so benumbed by a suppository containing iodoform that defecation may take place without the knowledge of the individual. Although it does not, itself, possess any germicidal properties, by decomposition and formation of new compounds, iodoform becomes a locally active substance. (See page 383).

*Absorption and Elimination.*—Iodoform, or the products of its decomposition, is absorbed very slowly from the alimentary canal, but is taken up from wounds with comparative freedom. It is largely destroyed in the system and escapes in a large part as an iodide and an iodate, but also partially as a new organic compound of iodine. Zeller believes that there is always an albuminous compound of iodine formed at the seat of absorption. According to the researches of Rummo, the elimination of iodine commences within one hour after the stomachic ingestion of the iodoform, and goes on so slowly that the haloid can be found in the urine three days later.\*

*Physiological Action.*—Notwithstanding numerous experiments upon the lower animals, further research is necessary before any positive knowledge can be reached as to the physiological action of iodoform, although it is probable that it acts very much as does iodine.

The symptoms produced by iodoform in the frog are said to be muscular relaxation with sometimes, at a later stage, convulsive movements. In the higher animals large but non-toxic doses produce symptoms of intoxication, tottering, weakness, and loss of appetite, but no vomiting; fatal doses cause anesthesia, narcosis, convulsions, with violent opisthotonos, hurried or irregular breathing, slow, feeble pulse, and finally death. A. Höyges found that in dogs and cats toxic doses caused deep sleep without loss of reflex activity, but that in rabbits no sleep resulted. Very frequently after these large doses, especially when they are repeated, there is great gastro-intestinal disturbance, as is shown by vomiting, diarrhœa, and dysentery, with bloody discharges. The action of the drug upon the circulation has been especially studied by Rummo. He finds that in the frog the rate of the cardiac pulsations is lessened, and for a time the energy of the ventricular systole is increased, but afterwards the pulsations become feeble, and finally the heart is arrested in diastole; the contractions cannot be re-established by the use of atropine. In the mammal the pulse is decreased, and after small doses the arterial pressure is at first increased. By large doses the pressure is much diminished. Section of the pneumogastries does not affect the cardiac action of the drug. After very large doses there are albuminuria and even hematuria.

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\* For an important bibliography, see the paper of M. Rummo. For details as to elimination and discussion of methods of finding the iodine in the urine, consult Harnack (*Zeits. f. Physiol. Chem.*, 1884, viii. 155), A. Zeller and E. Baumann (*Verhandl. Deutsch. Gesell. f. Chemie*, Berlin, 1882, xi. 219).

These various researches would indicate that the iodic compounds liberated by iodoform are universal poisons, and that the conclusion of Rummo is correct,—namely, that iodoform acts upon almost all the tissues, but primarily upon the nerve-centres and subsequently upon the nerve-trunks and on the muscles.

**Therapeutics.**—At one time iodoform was used to a considerable extent as an internal alterative and analgesic in *chronic syphilis*, especially when there were severe *rheumatic*, *neuralgic*, or *night-pains*. It has also been employed as an absorbefacient substitute for iodine in various *lymphatic tumors* and *serous effusions*. It seems to have, however, no superiority over the simpler iodine preparations, and to be much less certain and definite in its action, so that its internal use has passed completely out of vogue.

On the other hand, as a local remedy, it has continuously asserted itself in the face of very numerous substitutes, and is still largely used. It is useful in cases of painful *ulcers*, even when they are *cancerous*, serving to alleviate pain and to promote cicatrization. At first employed especially in *syphilitic affections*, it is now known to act equally well in *indolent leg ulcers*, in *burns*,\* and in other non-specific abrasions, and it is thought to be not only a local anesthetic, but also a decided stimulant to nutrition. Within the last few years it has been very freely employed as an antiseptic dressing to *wounds*, and the testimony is so strong that it is difficult to avoid believing that it is one of the most reliable of the antiseptics. It is employed either in the form of powder dusted in the wound, or as dressings saturated with it, the first method being at once the more effective and the more dangerous.

As a local anesthetic it is especially useful in rectal diseases, as *hemorrhoids* and *anal fissures*. It may be applied as an ointment or in the form of a suppository.

The danger of iodoform-poisoning in a surgical case varies not only with the amount of iodoform used, but also with the form of the iodoform and the seat of the application. The more finely powdered the iodoform the greater its activity, and serious absorption is especially likely to take place from the peritoneal surfaces.†

In 1886 Fürst described furuncular and eczematous inflammation produced by the contact of iodoform with the skin. Krevet affirms that this irritation can rapidly be relieved by momentary applications of very hot water to the part.

The good results which have followed the surgical use of iodoform as an antiseptic dressing have led to a series of investigations as to

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\* *Burns, Treatment of.*—At a discussion of the International Congress of Dermatology, in 1889, the conclusion was reached that the best treatment of burns in the beginning is to cut the bullæ, wash the part with a very weak solution of salt, and then dress with iodoform gauze, or a pomade of iodoform, and cover with oil-silk. In the later stages, after the separation of the eschars, according to Hebra, iodoform retards cicatrization while a one- or two-per-cent. solution of resorcin hastens epithelium formation.

† In a case in which an extensive intra-peritoneal dressing of iodoform gauze was used, and seven grains of calomel given by the mouth, violent irritant poisoning, with numerous bloody mucous stools at short intervals, occurred, evidently as the result of the formation of the mercurous iodide in the alimentary canal.—F. F. Simpson in a letter.



its action on the lower organisms, with results which are apparently at variance with previous surgical teachings. In November, 1886, De Ruyter announced at a meeting of the Berlin Surgical Society that the powder of iodoform has little or no effect in preventing the development of bacteria, and that when it is mixed with rapidly infective bacteria, like those of anthrax, it does not sensibly influence the development of the disease which is caused by inoculation with the mixture.

This has been confirmed experimentally by Kronacher, who employed the bacteria of erysipelas and of anthrax; also by P. Baumgarten,\* who further found that iodoform powder mixed with the tubercle bacillus in cultivating apparatus did not prevent its ordinary development, and that the bacillus mixed with iodoform powder when introduced into guinea-pigs and rabbits produced rapid tuberculosis; also by Lübbert, with the *Staphylococcus pyogenes*; also by Heyn and Thorkil Drowsing, who found that iodoform has no influence upon the development of the *Staphylococcus pyogenes* or of the coccus of pneumonia or of the *Bacillus subtilis* and other organisms, and conclude that it is not only worthless as an antiseptic, but may even be the means of carrying the septic organisms into the system; also by Johann Olsen, with various bacterial organisms; also by Könige. On the other hand, H. Sattler, in his experiments, found that when he impregnated threads with iodoform and micro-organisms and then placed them in culture-apparatus, the iodoform had a very distinct effect in checking the development of the bacteria, and De Ruyter states that if instead of using the iodoform powder he employed an ethereal solution in which decomposition of the iodoform had already commenced, there was a distinct effect upon the organisms. In a further series of experiments De Ruyter showed that iodoform is decomposed by blood, serum, and other organic fluids in which micro-organisms are growing, and apparently proved that the decomposition is produced by the ptomaines developed by the growing organisms. These general results have been abundantly confirmed; † the antiseptic properties of iodoform depend upon its decomposition, and its action is most favorable when the processes of fermentation and of chemical activity are most energetic.‡

The clinical results achieved by surgeons are so concordant and so decided that the practical value of iodoform in the treatment of wounds and ulcers must be considered established. It is possible that a part of the good influence of the iodoform is due to a specific effect upon the tissues of the wounds. Further, the powder of iodoform may have a very distinct protecting power both mechanically and by the dryness of the wound which it maintains, the discharges from the wound being the especial soil in which the bacteria develop. In tubercular diseases iodoform appears to exert a direct influence upon the bacilli. Many clinicians bear strong testimony to the effect of iodoform on *tubercular ulcers* of the larynx and other organs. According to Bruns, the first change which results from the use of iodoform in a tubercular abscess is the disappearance of the bacilli and appear-

\* A curious fact made out by Baumgarten was that rubbing the bacillus of anthrax with any hard powder apparently mechanically kills the organism.

† See especially Neisser (*Virchow's Archiv*, ex.), Schnirer (*Wien. Med. Presse*, 1887, ex.), and Kuntz (*Beitrage Path. Anat. u. Physiolog.*, 1888, ii.). According to the experiments of Altenberg (*A. I. P. T.*, 1901, viii.), the blood, serum, and urine do not liberate free iodine from iodoform, although the tissues of various organs, even when dried and powdered, have the property of so doing. It seems to us probable that these tissues depend for their activity upon the presence of micro-organisms.

‡ Moeller has found that the *iodates* and *iodic acid* cause symptoms similar to those produced by iodine (*Inaug. Diss.*, Bonn, 1877), and Schwerin has shown that *methyl iodide* is also anesthetic and hypnotic (*Centralbl. f. Med. Wissenschaft.*, 1884, 146).

ance of the normal granular tissues. The value of iodoform as a local application in surgical tuberculosis seems to be firmly established. In the treatment of *tuberculous abscesses*, in *tuberculous empyema*, in *tuberculous joints*, in non-suppurating *tuberculous glands*, and even in *tuberculous peritonitis* numerous cures have been reported. That the iodoform has a specific influence upon the tubercular organism would seem to follow from the experiments of Gosselin, of Caen, who found that guinea-pigs saturated with iodoform are incapable of contracting tuberculosis. The manner of application varies with different surgeons. Verneuil, who has had an enormous experience, prefers, in the treatment of abscesses, tuberculous glands, and in most other cases, the injection of a five-per-cent. ethereal solution. Others prefer glycerin as a menstruum, especially in empyema; while others, particularly in peritonitis, dust the dry powder over the portion which has been laid open.

**Administration.**—Iodoform may be applied to ulcers in powder, in solution, or in ointment. When there is a great deal of pain, especially if there be much discharge, the powder is to be preferred; not more than half a drachm of iodoform should ordinarily be applied to a wound, although in cases of *tuberculosis* the surgeon is more than warranted in taking the risk of larger amounts. Verneuil injects at one sitting never more than seventy-five grains of the iodoform. There is certainly much truth in the criticism of Kobert, that probably in most cases one-tenth part of the amount of iodoform habitually employed by the surgeon would suffice for all therapeutic purposes, and that many lives are unnecessarily endangered by the excessive amount of the drug used. In *uterine cancer* and in painful *hemorrhoids* cacao-butter suppositories, containing from five to ten grains of the drug, may be employed. They are also often very valuable in relieving *dysenteric* and various irritable neurotic conditions of the rectum. Owing to the bad odor of the drug, its application about the mouth and throat is often objected to.

According to Lewis Elsberg, if to four parts of absolute ether one part of crystallized iodoform be added, and the whole shaken in a *red* glass flask, a solution is obtained of sufficient strength for effectual use in diseases of the mouth, and free from odor other than that of ether. Olive oil, saturated with camphor, is said to dissolve six per cent. of iodoform, and is preferred by some surgeons.

**Toxicology.**—In the largest therapeutic doses (five to six grains) iodoform produces no symptoms, and we know of no cases of poisoning by its internal administration. On the other hand, its surgical use has led to a number of fatal poisonings. The symptoms, as recorded, have been very various. They may be preceded by general malaise for a day, and then suddenly burst forth.\* In the most characteristic and severe class of cases the phenomena resemble somewhat those of meningitis, and may be somnolence, deepening

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\* Case, *Deutsch. Med. Wochenschr.*, ix., 443.

into stupor, with contracted, motionless pupils, or restlessness, ending in active delirium, in either case the temperature being normal and the pulse exceedingly rapid. A peculiarity of these cases seems to be that death usually follows, although the symptoms have developed abruptly and the dressings have been removed at once. Schede, of Hamburg, describes six classes of cases, his sixth form being that just spoken of. 1. High fever, without other phenomena. 2. Fever, with mild gastro-intestinal irritation, depression of spirits, and rapid pulse; recovery almost invariable. 3. Very rapid, soft pulse, 150 to 180, no fever; great danger. 4. Very rapid pulse, with high fever; death almost invariable. 5. After severe operations, rapid collapse and death. A form of poisoning with melancholia, dilated pupils, and hallucinations is also described. A roseola-like dark red eruption has been noted in some cases of poisoning (Anschutz has seen violent acne); even when the constitutional symptoms are very slight there may be an extensive erythema.\* Convalescence may be very protracted, the patient remaining in a condition of unconsciousness or semi-consciousness for some days, with complete loss of memory and some evidences of mental disturbance. According to De Schweinitz, iodoform has rarely produced amaurosis or amblyopia with scotomata.

On account of the indefiniteness of the symptoms of iodoform-poisoning great importance attaches to any positive means of recognizing the nature of the illness. Burlureaux affirms that if a piece of silver be placed in the mouth of a person suffering from iodoform-intoxication, the taste of garlic will be immediately perceived, and that if some of the saliva be mixed with calomel, a canary-yellow precipitate of mercurous iodide will be obtained; according to Sasse, if a pinch of powdered calomel be placed upon a saucer, and a few drops of the urine from a case of iodoform-poisoning be mixed with it by means of a glass rod, the yellow color will appear (yellow iodide). These tests prove only that the patient is under the influence of some compound of iodine, but, if correct, must in many cases be sufficient for the purposes of the practitioner.

After death from iodoform a very wide-spread fatty degeneration is to be found. This change appears to commence in the liver and rapidly to involve all tissues of the body. Floucaud states that there is a very distinct alteration of the blood-corpuscles.

The quantity required to take life is uncertain. Langenstein attributes a death to four grammes; the cause of the death seems, however, doubtful. Czerny reports death from six grammes.

*Treatment.*—Whenever any suspicious symptoms arise during the use of iodoform, the dressing should immediately be removed and the part well washed with warm water. The assertion by Sampter and Retzlaff that the potassium bromide is a chemical antidote by virtue of its dissolving iodine compounds, has, so far as we know,

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\* Cases, *Intern. Cong., Copenhagen, 1884, Sect. Dermatol., 118.*



received no clinical or experimental confirmation, and there appears to be no other treatment of iodoform-poisoning than the free internal use of water, with the hope of aiding in the elimination of iodine compounds and the meeting of symptoms as they arise.

### IODOL.

*Tetra-iodopyrrol* or *iodol*, which is made by the action of iodine upon pyrrol, is a yellowish-brown, shining powder, composed of long, prismatic crystals, soluble in three parts of soluble alcohol, in ether, and in fatty oils, but soluble in water only in the proportion of 1 to 5000. It is tasteless and without odor. It contains 88.9 per cent. of iodine, as contrasted with 96.7 parts contained in iodoform. First discovered by Silber and Ciammican, it was proposed as an antiseptic by G. Mazzoni, of Rome. It causes in the lower animals (Marcus and T. Pahl) emaciation, albuminous urine, fall of temperature, general loss of muscular power, and finally death from fatty degeneration of the liver, kidneys, and other tissues. The assertion that it is not capable of producing constitutional symptoms is not correct. C. Langenstein reports, as caused by the surgical use of the drug, dizziness, marked rise in the temperature, vomiting, small irregular pulse of 136 per minute, albuminous urine, and apathy, which did not subside for four days. Iodine was found in the urine for two weeks.

In the experiments of Seifert, iodine was first detected in the urine and saliva twelve hours after the ingestion of seven and a half grains, did not reach its maximum until eighteen hours, and continued present for three full days; this accords with the statement of Pick that iodol is absorbed very slowly. This slow absorption is probably the reason that it is a less dangerous topical application than is iodoform.

Cervesato affirms, with doubtful correctness, that in man iodol, taken internally, acts like iodine preparations, but never causes iodism.

**Therapeutic Use.**—Iodol may be employed for all purposes for which iodoform has been used. Mazzoni's solution was: iodol one part, alcohol sixteen parts, glycerin thirty-four parts. One drachm of iodol forms with one ounce of ether a clear brown solution, which may be applied by the spray or brush to the nasal and other mucous membranes, upon which it leaves a coating of iodol. Iodol has also been used as an internal remedy. According to Assaky, iodol is very effective in *tertiary syphilis* in doses of from six to thirty grains (0.4–2 Gm.) a day.

### THYMOL IODIDE.

*Dithymol-Diiodide* frequently called by the trade name of Aristol, containing 45 per cent. of iodine, is a light, reddish-brown, crystalline powder, with a slight aromatic odor, insoluble in water, very soluble in fats and ether, slightly soluble in alcohol. According to Neisser, Quinquaud and Fournioux, and Eichhoff, when introduced even in very large amounts into mammals it produces no serious intoxica-

tion. The method of its elimination has not been made out. Quinquaud and Fournioux succeeded in demonstrating the presence of iodine in the urine of animals to which it has been freely given, but were not able to discover traces of thymol. The experiments of Neisser seem to show that it has no influence upon the lower organisms, and it cannot be considered, therefore, as directly antiseptic. It has been employed by a number of practitioners with asserted good results as a local application in inflammations of the mucous membranes of the nose and upper air-passages, especially when there is absence of secretion; also in *psoriasis*, in *lupus*, in various *syphilitic lesions*, and as a substitute for iodoform in the treatment of *wounds*. It appears to be free from irritant properties, and may be used in a strength varying from ten per cent. to the pure powder.

Through the ingenuity of pharmaceutical chemists there have been put upon the market a number of iodine compounds, very few of which have real value.

NOSOPHEN, the acid *tetra-iodo-phenol-phthalein*, is an impalpable, yellow-gray, odorless, tasteless, insoluble powder, containing sixty-one and seven-tenths per cent. of iodine. Its sodium salt, *Antinosine*, is a dark blue amorphous powder, readily soluble in water and alcohol. Its bismuth salt, *Eudoxine*, is a reddish-yellow, tasteless, odorless, insoluble powder. It is alleged that nosophen and antinosine are not decomposed in the human body, while eudoxine is slowly changed by the alkaline juices of the intestines into antinosine and bismuth. It is alleged also that they are germicides. As intestinal antiseptics, eudoxine being the best, they may be given in doses of five to eight grains (0.3–0.5 Gm.).

Locally, antinosine, on account of its solubility, is preferred as an application in infective inflammations of the mucous membrane, the strength of its solution varying from one to three per cent. According to Binz and Zantz, when given intravenously, antinosine is decomposed and nosophen precipitated in the blood.

EUROPHEN, *di-isobutyl-ortho-cresol-iodide*, is a yellowish amorphous powder, containing twenty-eight and one-tenth per cent. of iodine, which is stated to be decomposed more slowly than iodoform, and to be therefore less poisonous. Taken internally, it escapes unchanged in great part or altogether with the feces, and is said to be non-toxic, fifteen grains producing no effect in human beings. Externally, it has been employed to a considerable extent as a substitute for iodoform, but appears to have some irritant properties.

SOZIODOL, *di-iodoparaphenolsulphonic acid*, contains thirty-one and a half per cent. of mercury and thirty-eight per cent. of iodine; it has been used as a local irritant, chiefly employed in the form of a powder (talc), fifteen per cent. The assertion of A. Lübbert, that it is as active as corrosive sublimate as a germicide, and free from poisonous properties, has not been confirmed.

IODOFORMOGEN, a compound of albumin and iodoform, nearly free from odor, is a light yellow powder, insoluble in water, which has been used as a substitute for iodoform.

### COD-LIVER OIL.

Cod-liver oil is obtained from the liver of *Gadus morrhua* and of other species of *Gadus*. In the manufacture of the so-called *Shore oil*, the only variety employed in medicine, the fish caught near land are brought at once to the shore, and the oil is obtained by forcing steam at high pressure through a mass of the fresh livers enclosed in

a metallic vessel, so as to tear them into pieces and melt out the oil. Cod-liver oil for medicinal purposes should always be perfectly limpid, yellow, free from rancidity, and have the peculiar taste and smell of the oil well developed. The cruder varieties, sometimes known as *Straits* or *Banks oil*, used in the preparation of leather and for other purposes in the arts, are prepared by allowing the livers to stand in casks and undergo putrefaction until the oil rises to the top, when it is skimmed off. The black or brown oil which results is extremely disgusting both in odor and taste, and is loaded with the products of decomposition.

Cod-liver oil is a very complex substance, containing glycerin, oleic, margaric, butyric, and acetic acids, gaduin, various biliary principles, iodine, chlorine, traces of bromine, phosphorus, phosphoric acid, and a peculiar ammoniacal base, trimethylamine (commercial propylamine), which exists in no other official oil, but occurs in ergot. According to the U. S. Dispensatory, the proportion of iodine never exceeds 1 part in 2000. *Gaduin* is a peculiar, dark brown substance, which is probably medicinally inert.

#### Official Preparations :

Oleum Morrhue.....	1 to 4 fluidrachms (4-15 C.c.).
Emulsum Olei Morrhue (50 per cent.).....	1 to 8 fluidrachms (4-30 C.c.).
Emulsum Olei Morrhue cum Hypophosphi- tibus (50 per cent.).....	1 to 8 fluidrachms (4-30 C.c.).

**Physiological Action.**—As is well known, all fatty substances when taken into the system have a tendency to cause deposition or formation of fat in the body. Cod-liver oil certainly shares this property in an eminent degree. Pollock (quoted by Stillé) has found that if there be given of it to pigs from one to two ounces *per diem*, to sheep one ounce, and to bullocks from three to nine ounces, it is digested, and aids in fattening the animal; larger amounts than those noted in Pollock's experiments always derange very seriously the digestive function. No close studies of the effect of the cod-liver oil upon healthy men have been made. Undoubtedly it tends to produce obesity; but, as no other oil is able to supply its place in various chronic diseases, it must have some influence upon nutrition not shared by ordinary fatty matters, and therefore is an *alterative*.

The history of the clinical use of cod liver oil certainly indicates that it influences the constitution of the blood. It is an every-day occurrence to see pale, anemic patients become, while taking it, rosy and plethoric. According to the analysis of the blood of a patient made by Simon, there is, during its use in *phthisis*, a great increase in the amount of solids in the blood, a diminution of the fibrin, and an increase in the albumin. The examinations of Dugald Campbell have confirmed the results of Simon. It is very probable that cod-liver oil has some peculiar influence upon the blood-making organs. Upon the various single functions of the body, except the digestive, cod-liver oil has no apparent immediate effect, disturbing directly



neither the nervous, motor, respiratory, circulatory, nor secretory movements. When by its use the general nutrition is improved, all the functions seem to share equally in the improvement. Cod-liver oil has undoubtedly, when given with sufficient freedom, a tendency to cause indigestion and looseness of the bowels. All oils are of difficult digestion, and when too much of the *oleum morrhuae* is exhibited in man, as in animals, it exerts a deleterious local effect upon the alimentary apparatus.

Much speculation has been indulged in as to which of the ingredients of cod-liver oil impart to its peculiar medicinal properties.\* Certainly, however, no conclusion has been established, and the present probabilities are that it acts as a whole,—*i.e.*, that its virtues depend upon the peculiar combination.

The experiments of Oswald Naumann indicate that the physical properties of cod-liver oil aid in its usefulness. He first tested the rate at which various oils pass through fresh moist animal membranes when pressed upon by a column of mercury or by the weight of the atmosphere over an exhausted receiver, and found that cod-liver oil passed much more rapidly than did any of a number of oils tried. Apparently this power depended in some measure upon the presence of the biliary principles, since if it was deprived of them the rate of its passage was greatly lessened, but was again increased by the addition of a little bile. The investigator then, opening the abdomen of cats, separated in each animal by ligatures two knuckles, of equal length and entirely similar, from the remainder of the intestines. Into each of them he injected a certain amount of bile, and then into one ordinary oil, into the other cod-liver oil; and when the animals died, some hours afterwards, it was always found that much more of the cod-liver oil was absorbed than of the other oil. Naumann's experiments were too few and incomplete to be decisive, but they accord with the clinical observation of Berthé, who found that cod-liver oil could be taken longer than other fats without appearing in the feces; observations which have been confirmed by Bucheim, as well as by J. Gad. Both Bucheim and Gad believe that this absorability depends largely upon the presence of free fatty acids in the oil, but it is probably due to the biliary matter, since H. A. Hare finds it greatly increased by the addition of taurocholate and glycocholate of sodium. Hare asserts that cod-liver oil impregnated with a small quantity of the biliary salts is rapidly absorbed when rubbed upon the skin, and proposes the practical use of the mixture.

Naumann's last series of experiments were directed to discovering the comparative ease with which animal oils and the cod-liver oil were oxidized. For this purpose he used a test-solution of potassium permanganate, and on adding to given bulks of this, in test-tubes, equal amounts of the various oils, noted the changes of color induced by the reduction of the permanganate. He found that cod-liver oil was the first to be affected.

It is evident that the power of being easily absorbed and easily oxidized fits a fat for use in the animal economy; but even if cod-liver oil possesses these properties to a remarkable degree, it is clear that they cannot be the chief causes of its peculiar influence on disease.

**Therapeutics.**—Cod-liver oil is a valuable remedy in various conditions of emaciation not dependent upon diseases of the ali-

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\* A Gautier and J. Bouillot assert that they have found in cod-liver oil certain alkaloids which are stimulants to the circulation and to the nutrition, and also to the kidneys, and to which are largely or altogether due the peculiar properties of the oil. These alkaloids have been used in practical medicine by J. Bouillot, who affirms that 0.15 to 0.25 gramme given during the twenty-four hours powerfully stimulates nutrition, increasing very much the amount of the urine and also the nitrogenous elimination, especially of the completely oxidized nitrogen.

mentary canal or upon cancerous affections. It has been extensively used in various forms of *scrofula* and *tuberculosis* and where it does not disturb digestion is useful as a food of high caloric value. It has, however, no specific relations with the tubercle bacillus, acting only by stimulating the nutrition of the human organism. It is similarly effective in various non-tubercular conditions of defective nutrition as it is in phthisis. It is especially valuable in *rickets*. It is often of service in advanced *tertiary syphilis* with wasting cachexia. It first achieved its reputation as a remedy in *chronic rheumatism*. In *neuralgia* and in *various skin diseases* it may at times be used with great advantage. It is not the disease, but the general condition of the nutrition which should influence the practitioner in the employment of this remedy.

**Administration.**—The chief difficulty in the use of cod-liver oil is the very common, real or imagined, inability of the patient to take it. Without doubt, this very often arises from its nauseous taste, to lessen or disguise which various expedients are resorted to.

Sometimes a piece of salt taken into the mouth just before the oil, which is also immediately followed by another lump of salt, suffices. It is said that some prefer the oil in emulsion made with some strong aromatic water. The addition of an equal part of glycerin and one-half to one drop of the oil of bitter almonds to the dose certainly lessens the taste of the medicine. In cases where alcohol is also indicated a successful plan of exhibition is to place, according to the exigencies of the case, from one to three tablespoonfuls of whisky or brandy in a tumbler, add a small amount of water, put the oil in the centre, and *toss* the whole down the throat, the head being held well back, the mouth wide open, and the lips not touched by the medicine. The stimulus of the alcohol often enables the stomach to digest the oil when otherwise it could not do so. Sometimes it is necessary to commence with a single small daily dose, even a single teaspoonful, which is best taken at bedtime, and gradually to increase the amount as the patient becomes habituated to it. Children almost always learn to tolerate the taste of the oil, or even become in a short time fond of it.

When infants cannot digest cod-liver oil, inunctions may sometimes be practised with advantage. N. A. Randolph and A. E. Roussel state that they have seen, in such cases, the oil appear in the feces.

### COLCHICUM.

*Colchicum autumnale* or meadow saffron, is a small plant belonging to the lily family, found in Europe and England. The official portions are the seeds and the corm. The latter which is often incorrectly called the root, is the thickened, swollen end of the stem with the little tuber attached, whose office it to develop a new plant. This *corm* is solid and fleshy, an inch and a half to two and a half inches in length, with a longitudinal groove, having a nail-like process (the bulblet) at its base. In the shops it is very commonly kept in transverse slices, which are notched and cordate; the taste is bitter, hot, and acrid. *Colchium* seeds are nearly round, about an eighth of an inch in diameter, and of a bitter, acrid taste. *Colchicum* depends

for its activity upon the presence of an alkaloid *colchicine*,\* of which the seeds should contain 0.45 per cent. and the corm, 0.35 per cent. Colchicine exists in the form of pale yellowish globules, or as an amorphous powder. It is soluble in 22 parts of water, freely soluble in alcohol and chloroform.

#### Official Preparations:

Fluidextractum Colchici Seminis.....	2 to 6 minims (0.1–0.4 C.c.).
Tinctura Colchici Seminis (10 per cent.)... $\frac{1}{2}$	to 1 fluidrachm (2–4 C.c.).
Vinum Colchici Seminis (10 per cent.)... $\frac{1}{2}$	to 1 fluidrachm (2–4 C.c.).
Extractum Colchici Cormi.....	$\frac{1}{2}$ to 2 grains (0.03–0.10 Gm.).
Colchicina.....	$\frac{1}{100}$ to $\frac{1}{50}$ grain (0.6–1.3 Milligm.).

**Local Action.**—**Absorption.**—**Elimination.**—Although preparations of colchicum brought in immediate contact with the mucous membrane do not seem to be immediately and actively irritant, yet when taken internally they produce violent gastro-intestinal irritation which is probably closely connected with attempts at elimination. Concerning the elimination of the active principle of the drug we have little knowledge, although it can scarcely be gainsaid that the alkaloid escapes with the urine and, when in toxic dose, probably more largely with the gastro-intestinal secretions.

**Physiological Action.**—No distinct symptoms are produced by the smallest therapeutic doses of colchicum. After somewhat larger amounts there is gastro-intestinal disturbance, as shown by abdominal uneasiness, colicky pains, borborygmi, loss of appetite, moderate purging, and sometimes nausea,—symptoms differing in degree only from those of poisoning by the drug. Before these come on, however, there is a lowering of the pulse-rate, sometimes as much as twelve beats per minute, which, according to some authorities, is sometimes accompanied by free diaphoresis, though it has never been our experience to see this symptom. Any nervous symptoms, such as vertigo, headache, or muscular weakness, which may be present as the result of the administration of colchicum are probably sympathetic from the gastro-intestinal irritation.

The physiological effect of a single full dose of colchicum is not yet clearly demonstrated and is, from a practical standpoint, of com-

\* The active principle of colchicum is without doubt colchicine. See Geiger (*Annal. Chem. Pharm.*, vii. 274), Hoppe, Aschoff (*Vierteljahresschrift f. Prakt. Pharm.*, vi.), Schrott (*Oester. Zeitschrift f. Prakt. Heilk.*, 1856), and Albers (*Deutsche Klinik*, 1856, xxxvi.). Jacobi affirms that absolutely pure colchicine is physiologically inert, but that it is transformed in the system into a brown, amorphous, oxidation product, *oxydicolchicine*, which produces the poisoning symptoms commonly attributed to colchicine.

*Colchicine* is a neutral crystallizable substance, soluble in water, which is produced by the action of mineral acids and certain other agencies upon colchicine. Its toxic influence has been studied upon dogs by Samuel R. Percy (*Amer. Med. Times*, April, 1862, 167), according to whom it produced symptoms very similar to those caused by colchicine; they are—*increase in the frequency of the pulse, severe purging with tenesmus, vomiting, finally great slowing of the pulse and failure of the heart's action, and death without convulsions.* The urine, at first increased, was afterwards suppressed. On post-mortem examination, the mucous membrane of the intestines was found highly inflamed, that of the stomach slightly so, and the heart and arteries were filled with black tarry blood, similar to that of colchicine-poisoning. On the other hand, Paschkis asserts that one and a half grains of colchicine injected into the jugular vein of a dog produced no results whatever. It is evident that the two experimenters had different substances. Ferrer (*University Med. Mag.*) found that colchicine acts chiefly upon the motor, and not, as does colchicine, upon the sensory nerves, and that while it stimulates the peripheral vagi, it does not depress the heart-muscle. S. R. Percy affirms that in gout colchicine increases the elimination of urea and of uric acid, but his experiments are too few to be decisive.



paratively little interest. According to both Rossbach, and Adolfo Ferrer y Leon, it has very little action upon the circulation, although Schaitanoff and Paschkis state that the drug notably increases the arterial pressure. It has a distinct depressant action upon the nervous system affecting especially the sensory nerves, and to a lesser extent also the spinal cord. Dixon states that it causes a marked leucocytosis. Kionka asserts that colchicine causes a marked increase in the secretion of bile.

Upon most animals toxic doses of colchicum acts very much as it does upon man, in poisonous doses producing, as prominent symptoms, severe and often bloody purging, vomiting, great prostration, embarrassed respiration, finally more or less pronounced paralysis, and death, not rarely preceded by convulsions. Reflex actions are lessened and finally abolished (Albers, Rossbach) in the frog; but Rossbach affirms that there is a precedent stage of convulsions with excessive reflex activity; in warm-blooded animals this first stage of excitement is rarely, if ever, seen.

The force of the poison is chiefly expended upon the alimentary canal, which is always found, at least in mammals, to be in a condition of intense inflammation, even when colchicine has been given hypodermically.

The relief which is afforded in a gouty condition by purgative doses of colchicum can hardly be explained by the supposition that the drug causes the elimination of gout-poisons through the bowels, because the effects produced by doses too minute to act upon the gastrointestinal tract are often decisive; so that great interest attaches to the question as to the influence of the drug upon the kidneys. It is certain that sometimes the continuous moderate use of colchicum distinctly increases the flow of urine, but its action is not invariable, and, unfortunately, the question as to whether the drug notably increases the elimination of solid materials from the urine cannot at present be answered with definiteness, the testimony in regard to the action of colchicum upon the elimination of urea and uric acid in health and in disease being too contradictory and insufficient to warrant any conclusion.

Thus, Bird quotes Krahmer's experiments as showing that colchicum does not increase the amount of solids eliminated in health, and intimates that his own investigations had given similar results; while Hammond, on the other hand, in a series of experiments in which every care to avoid fallacies, by maintaining equality as to diet and exercise, was observed, found that while squill and digitalis increased only the watery part of the urine, both the organic and the inorganic solids were remarkably augmented by colchicum.

The testimony as to the effects of the drug in disease is no less discordant. In 1828 Chelius announced that during its administration in gout the amount of uric acid eliminated is nearly doubled. R. Lewins submitted the urine of several persons suffering from gout, taken before and after the administration of colchicum, to Christison, who found in the colchicum-urine the *proportion* of urea nearly double, and that of uric acid greater than, that of the other specimens.

In 1852 MacLagan analyzed the urine of three cases of rheumatism before and after the exhibition of colchicum: in two instances the *proportion* of urea was very greatly increased, that of uric acid slightly so. In the third case the effect just noted happened at first, but not afterwards.

On the other hand, Stillé states that Graves and Gardner affirm that the urates diminish under the use of the medicine. It is evident that these different results are not so contradictory as they seem, for it is possible that in one case the colchicum may so act as to increase the elimination of urea, in another that of uric acid, and that when one of these is increased the other may be unaffected, or even diminished.

Further, when the medicine purges freely it is very probable that elimination by the kidneys is lessened; and no account of this is taken by any of the observers whose original papers we have seen. Moreover, these observers also all contented themselves with noting the proportion of urea and uric acid in the urine, when it is evident that the mere proportion, unchecked by the absolute amount of urine secreted during the twenty-four hours, is no criterion as to the absolute amount eliminated. A. B. Garrod has made a study of the subject in such a way as to avoid this fallacy, and found that the elimination of urea and uric acid was sometimes increased, but that, on the whole, no marked effect was produced. Noel Patton states that in his experiments on dogs small doses of colchicum increased very distinctly the elimination of urea and uric acid, as well as the amount of the urine; while large doses lessened the amount of urinary secretion and increased slightly the daily elimination of urea and uric acid. He believes that the increase was due to an increased production, because after the administration of the drug the daily elimination did not fall below the normal. We do not think, however, that at present we are warranted in considering it established that colchicum materially influences nitrogenous elimination.

**Therapeutics.**—Colchicum is of no value in practical medicine save for the treatment of *gout*, in which disease it has long been recognized as a specific. Our acquaintance with its physiological action is not sufficiently positive to establish any theory as to the method in which the drug acts. It may be that it simply increases the throwing off of gout-poisons, but this is not proved. The theory advocated by Hugo Schulz, that it increases very greatly the circulation in the capillaries of the muscles and joints, and thereby brings relief in gouty states of passive congestion, and causes absorption of gouty exudates, is ingenious, and may or may not be true.

Colchicum may be used to prevent the coming on of a gouty paroxysm, or to lessen the severity of the symptoms when the paroxysm has already been developed. During an attack of gout, from three to five minims (0.2–0.3 C.c.) of the fluidextract of colchicum seed may be exhibited every four hours until some decided evidence of its action, such as nausea or slight purging, is induced. It should always be borne in mind that although looseness of the bowels may be useful, yet severe purging is to be avoided. In some cases, especially in debilitated subjects, the action of the drug upon the bowels should be restrained by the use of opium or other medicament. By large purgative doses of colchicum the paroxysms of gout may often be suppressed; but experience has shown that this use of colchicum is dangerous, the suppression being sometimes followed by serious internal disease, apparently due to a transfer of the gouty irritation. Between the paroxysms colchicum may steadily be exhibited to the gouty subject in small doses, and often great advantage is derived from its combination with potassium iodide.

In *rheumatism* colchicum has been highly recommended, but is of little value. Colchicum has been administered in various diseases, but when there is no rheumatic or gouty taint is at present very rarely used.

**Toxicology.**—In poisonous doses colchicum produces violent purging, whose onset is soon followed by severe, often uncontrollable, vomiting. The discharges from the bowels are at first large and serous, but later become smaller, more mucous, with flaky deposits, and finally in some cases bloody. Abdominal pain may be absent or present, but if present is generally griping; sometimes there is gastric burning. Nervous symptoms have been prominent in some of the severe cases. In one instance, it is said, a feeling of numbness or prickling was complained of by the patient; but this seems not to be common. Spasms are very frequent, and sometimes convulsions, which may be fatal, are present. Muscular pains are not rarely experienced: in some cases replacing the spasms, and probably in all other cases coincident with them, is great muscular weakness, amounting, as death approaches, to paralysis. Finally, a condition of collapse develops, the circulation fails more and more, the pulse, which has been frequent and feeble, becomes rapid and thready, the skin cold, pale, or livid, and bedewed with sweat, and death from exhaustion results. Consciousness is preserved until the last. The effect of lethal doses of colchicum on the urinary secretion varies: sometimes the kidneys seem to be nearly unaffected almost to the last: sometimes their functional activity is decidedly increased, but in other cases it is diminished, and even suppression of urine has been noted.

After death from colchicum the blood is generally found very dark and imperfectly coagulable, but whether this is due to a direct action of the poison or is the result of the slow death by asphyxia and exhaustion has not been determined. The chief changes are, however, in the alimentary canal, the mucous membrane of which is much swollen, intensely congested, sometimes ecchymotic, or with blood free in the intestine.

As was first pointed out by Schroff, and since confirmed by Rossbach, the rapidity of death in colchicine-poisoning is not at all in proportion to the size of the dose. Thus, Schroff noticed that one and a half grains of colchicine produced death in the rabbit in fourteen hours, while fifteen grains killed in eleven hours. This failure of relation seems to be explicable only by the supposition that colchicine kills chiefly by its irritant action on the alimentary canal, and, not being in any dose corrosive, requires time to work out the fatal result, through the instrumentality of a gastro-enteritis. This deduction is confirmed by the long-protracted course of the poisoning after small doses. Thus, Aschoff noted death on the ninth day in a pigeon which had received one-fourth of a grain of the alkaloid.

The fatal dose varies, but is small. George B. Wood states that death has been produced by two drachms and a half of the wine of colchicum root, and Taylor records a case in which three drachms and a half proved fatal. On the other hand, recovery has taken place after the ingestion of an ounce.\* According to the experiments of Schroff, *colchicine* is eighty to one hundred times stronger than the fresh corm. According to Heinrich (quoted by Husemann),

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\* See case in *L'Union Médicale*, Aug. 1848.



0.15 grain of colchicine will produce poisonous symptoms in man, and in Krahmer's experiments 0.3 grain caused in an adult violent serous purging, lasting for four days, and accompanied by severe tenesmus. Casper has seen death result from a quantity of the wine containing 0.025 to 0.03 gramme (0.37–0.45 grain) of colchicine; but, according to Husemann, recovery has taken place after the ingestion of 0.045 gramme of the alkaloid.\* Suffet and Faastem report death in a case of nephritis from 0.003 gramme of colchicine dissolved in 2.40 grammes of methyl salicylate.

The treatment of colchicum-poisoning is as follows. If the stomach and bowels have not been freely evacuated, administer at once an emetic and a cathartic, so as to empty the alimentary canal; allow the patient to drink freely of warm water, to aid in these operations and to act on the kidneys. Give freely of tannic acid, as the only known chemical antidote, although experiments upon animals have shown that it is not to be relied upon. To check the vomiting and purging, administer opium freely; and to allay the irritation, cause the patient to drink freely of albuminous matter, such as white of egg dissolved in water: the tannic acid having been given as soon as possible after the taking of the poison, the demulcents are useful in the more advanced stages. Symptoms of gastro-enteritis or of collapse are to be met as they arise.

### ICHTHYOL.

Ichthyol is a substance first prepared by Schroeter by the distillation of a peculiar bituminous sulphurous mineral obtained from the deposits of fossil fish. It occurs in commerce in the form of *sodium ichthyo-sulphate* and *ammonium ichthyo-sulphate*. Ammonium ichthyol is a reddish-brown, clear, thick liquid, of a hot bituminous taste and smell, at a high heat burning without ash, making with water a clear, reddish-brown solution of a weak acid reaction, which, when treated with hydrochloric acid, yields a dark resinous precipitate. Sodium ichthyol is a dark, tar-like substance of an alkaline reaction, perfectly soluble in water. Both these preparations combine with fat and vaseline in all proportions. The ichthyol preparations are said to contain ten per cent. of sulphur.

**Therapeutics.**—According to Baumann and Schotten, ichthyol has little apparent action on the general system, and when given to dogs in doses of five drachms produces no symptoms save diarrhœa. As a local remedy it has been extravagantly praised by Unna, Kiesner, and a large number of German dermatologists and surgeons, and has also received strong encomiums in America. When applied freely in a pure form to the sound skin it produces slight irritation and

† George W. Major (*Canada Med. and Surg. Journ.*, Dec. 1873) records seventeen cases of poisoning from one bottle of wine of colchicum seeds, occurring in Montreal, seven of which proved fatal. The patients had been vomiting and purging almost continuously for many hours when first seen, and the symptoms were exactly those of the stage of collapse of severe cholera morbus. In no case was the purging bloody. Consciousness was preserved to the last, and in only one case was there anything like convulsions. There was decided numbness of the extremities, and a peculiar hoarseness of the voice was especially noted.

burning. It is asserted to have, when used as a local application, peculiar alterative properties, and also the power of penetrating through the skin so as to be able to act as an alterative anodyne and discutient in diseases not only of the skin but also of the subjacent tissues, probably having also germicidal powers. The cases in which it is of value are characterized generally by inflammatory enlargement or inflammatory pain.

In various skin diseases ichthyol has been used with alleged remarkable results,—in chronic *eczema*, chronic *urticaria*, *acne*, *intertrigo*, *lupus*, *keloid*, etc. In *lepra* Unna combines its internal and external use (dose, fifteen grains (1 Gm.) a day). It has also been recommended in the strongest terms for the relief of various *ulcerations of the skin* and for the prevention of *pitting in small-pox*, and also in *erysipelas*. In *lumbago* and other forms of *muscular rheumatism*, in *rheumatic* or *gouty joint disease*, indeed, in almost every form of subacute or chronic *gout*, according to Schweninger, Lorenz, and others, a few rubbings with pure ichthyol or a fifty per cent. ointment will produce an immediate and remarkable effect. It has been largely used in the treatment of *sprains*, *contusions*, *burns*, and *frost-bites*. If one-half that has been said of it be true, it is a local remedy of extraordinary power and value. Schmidt has even seen it soften and disperse a *lipoma*, and D. Hayes Agnew commends it very highly in the treatment of recent *lymphatic enlargements*. In sprains, when the skin is intact and not irritated, the ichthyol itself or a fifty per cent. ointment may be employed. In *erysipelas* Von Nussbaum covers the affected part, after thorough disinfection, with a thick layer of equal parts of ichthyol and petrolatum, and this in turn with a thick layer of salicylated cotton. The result is said to be immediate, the disease disappearing in a single day. In various skin diseases and ulcerations the strength of the application may vary from one to fifty per cent. Lorenz affirms that in acute *coryza* and inflammations of the nose or mouth a mixture of one to ten per cent. of ichthyol and petrolatum is very efficacious. Both Unna and Lorenz deny that it has any antiseptic properties.

*Ichthyol Albuminate*.—*Ichthalbin* is a greenish-brown powder, made by precipitating albumin with ichthyol, and containing seventy-five per cent. of ichthyol. It is insoluble in water, but soluble in alkaline solutions; it is odorless, almost tasteless, and has been highly praised in *syphilis* and in *scrofulous* conditions with lowered general nutrition. Dose, fifteen to thirty grains (1–2 Gm.) three times a day.

ISAROL, or *Ichthyodin*, made from crude ichthyol by the action of sulphuric acid, is said to contain about nine per cent. of sulphur, to be soluble in water and alcohol, and to be therapeutically equivalent to ichthyol. It has been commended as a substitute for refined ichthyol on account of cheapness.

SARSAPARILLA.—The roots of various species of *Smilax* inhabiting Mexico and northern South America have long been used in the treatment of chronic *syphilis* and chronic *scrofulas*. They contain three active glucosides belonging to the saponin group, namely, *parillin*, of Palotta; *saponin*, of Otten; *sarsaponin*, of Schulz.

To these glucosides, separate or combined, various names have been given by various investigators, such as *smilacin*, *salseparin*, *sarsaparillin*, and *sarillinic acid*. Of these glucosides, according to Kobert, sarsaponin is the most important, being the most active poison to the red blood-disks known. Palotta found that in doses of thirteen grains parillin causes vomiting and circulatory depression, but Böcker was unable to obtain such results, and there is no reason for supposing that the amount of these saponins in sarsaparilla is sufficient to give to the drug therapeutic activity.

**Official Preparations:**

Fluidextractum Sarsaparillæ.....	1 fluidrachm (4 C.c.).
Fluidextractum Sarsaparillæ Compositum .....	1 fluidrachm (4 C.c.).
Syrupus Sarsaparillæ Compositus.....	Vehicle.

Sarsaparilla has been used chiefly in the advanced stages of syphilis as an adjuvant to the mercurials and iodides, but its value is doubtful. If it is of service, it is in those cases in which the constitution is very much broken down by the disease. It is never used in substance; a *compound decoction* was formerly much employed, being modelled after the famous Lisbon diet-drink; it is equivalent to the present compound fluidextract diluted.

**GUAIAIC.**—*Guaiac resin* is believed to be diaphoretic and alterative, and has been much used in combination with sarsaparilla in chronic *syphilis*. In *subacute* and *chronic rheumatism* it is often of service. As suggested by William Murrell, ten to thirty grains of it (0.6–2 Gm.) may be given in electuary as an antirheumatic laxative in *tonsillitis* and *chronic rheumatism*.

Tinctura Guaiaci (20 per cent.).....	1 to 2 fluidrachms (4–8 C.c.).
Tinctura Guaiaci Ammoniata (20 per cent.)...	1 to 2 fluidrachms (4–8 C.c.).

**MEZEREUM.**—The bark of the *Daphne Mezereum* is said to contain a volatile acrid principle and the glucoside *daphnin*. In overdoses it is an active poison, producing, it may be, a fatal gastro-intestinal inflammation. In some cases the symptoms have been simply collapse, with unconsciousness, and other nervous disturbance (case in *British Med. Journ.*, 1882, ii. 521). Internally, mezereum has been used in combination with sarsaparilla; externally its *ointment*, formerly official, has been employed as a stimulant dressing to indolent ulcers.

Fluidextractum Mezerei.....	1 minim (0.06 C.c.).
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**TARAXACUM.**—The root of the common dandelion, *Taraxacum officinale*, is believed to have the property of altering the action of the liver, although no effect is to be witnessed from a single dose of the drug, however large,—other, at least, than some nausea. Diuretic properties have also been ascribed to taraxacum; but the only evidence brought forward to establish this is the vulgar name which the plant bears in both English and in French. If taraxacum be useful at all, it is in cases of *dyspepsia* in which there is habitual torpor of the liver, with constipation.

Fluidextract Taraxaci.....	2 to 3 fluidrachms (8–11 C.c.).
Extractum Taraxaci.....	15 to 30 grains (1–2 Gm.).

**STILLINGIA.**—*Queen's Root*.—*Stillingia* is said by Bichy to contain an alkaloid, *stillingine*. In overdose *stillingia* is an emeto-cathartic; it is used to a considerable extent as an alterative, especially in the class of cases in which sarsaparilla has been employed, often in combination with it.

Fluidextractum Stillingiæ.....	$\frac{1}{2}$ to 1 fluidrachm (2–4 C.c.).
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**XANTHOXYLUM.**—*Prickly Ash*.—The bark of two American species of *Xanthoxylum*, said to contain berberine and other alkaloids, is believed by various practitioners to resemble mezereum remedially, and has been especially useful in



chronic *rheumatism*. Externally xanthoxylum is sometimes useful as a mild counter-irritant; thus, in chronic *pelvic diseases*, much temporary relief is often obtained by a hot pack applied to the lower part of the trunk, made with four ounces of fluidextract of xanthoxylum and one ounce of tincture of cayenne pepper to two quarts of water.

Fluidextractum Xanthoxyli..... $\frac{1}{2}$  to 1 fluidrachm (2-4 C.c.).

JAMBUL.—The bark of the *Eugenia jambolana*, an East Indian tree, has long been used in India as a stomachic astringent in *diarrhœa* and as a specific in true *diabetes*. Its active principle has not been determined, but appears to be present in the bark, in the seeds, and also in the rind of the fruit; neither have we detailed knowledge as to the physiological action of the remedy.

Thomas Christy found that when sufficient diastatic matter was mixed with fifty grains of starch to convert forty-five per cent. of the latter in fifty minutes into sugar, the addition of twenty-five grains of powdered jambul seeds reduced the conversion of the starch eighty-eight per cent. In Binz's experiments, in dogs rendered diabetic by phloridzin, according to the method of Von Mehring, the exhibition of jambul reduced the excretion of sugar from fifty to ninety per cent. without producing any evidences of poisoning.

In human *glycosuria* jambul is usually without perceptible influence, but in some cases (literature and our own experience) its effects are more marked. It never produces any disagreeable effects, and from fifteen to forty-five minims (0.9-2.8 C.c.) may be given three times a day. Vix found that in doses of ten drachms (37 C.c.) a fluidextract made from the rind of the fruit acted efficiently as a diuretic.

THIOSINAMINE. *Allyl-sulphocarbamide*; *Allyl-sulpho-urea*; *Rhodalline*.—This substance, which is prepared from the oil of mustard, occurs in colorless monoclinic or rhombic crystals, of a bitter taste and feeble garlic-like odor. It is moderately soluble in water, very soluble in alcohol and ether. It possesses no bactericidal properties, and in the doses in which it has been used seems to exert no influence whatever upon the general system, except upon the blood-making organs. Several hours after its injection the leucocytes in the blood are greatly diminished in number, falling according to Hebra, in some cases from fourteen thousand to four thousand. This condition lasts, however, but a short time, and is followed by a pronounced hyperleucocytosis. During the latter period a very pronounced destruction and absorption of exudates and of cicatricial and other poorly nourished tissues are said to occur.

Thiosinamine was introduced into medicine by Von Hebra for the treatment of *lupus* and old *cicatrices* and has been used by many clinicians in *lupus*, *chronic glandular inflammations*, *scleroderma*, *keloid*, *urethral strictures*, *corneal opacities*, *plastic iritis* (G. F. Suker), and sclerotic conditions of the ear with consequent deafness. Una has also employed it locally in the form of a five to twenty per cent. soap or plaster in *fibrous tumors*, *keloid*, *leprous*, and *syphilitic lesions*, and for *small-pox scars*. Its local application may be continued for some hours, and is said not to produce irritation or pain. George E. de Schweinitz informs us that very extensive trials have forced him to the conclusion that the internal administration of thiosinamine is of no value whatever in any disease of the eye.

Dose, in capsule, one-half to three grains (0.03-0.2 Gm.); hypodermically, one to four grains in ten to fifteen per cent. alcoholic solution, preferably injected into the intracapsular or gluteal region; or, when the disease is superficial, in the neighborhood of the lesion. Considerable pain is said to be produced by the injection.

### LECITHIN.

Lecithin is a complex fatty body representing the phosphorus-holding molecule of the central nervous system. It occurs, however, not only in the higher animals but in many of the food-stuffs, and is especially abundant in embryonal tissues, as eggs and seeds. There are several varieties of lecithin so that the lecithin of eggs,

for example, is not chemically the same as that found in the human nervous system. The human lecithin is a *di-stearyl-glycerophosphate of cholin*, but any other fatty acid as oleic or palmitic, may be substituted for the stearic; thus we may have a palmityl or an oleyl lecithin. It is not probable that there is any marked difference in the physiological properties of the different forms of lecithin.

Lecithin occurs as a yellowish, waxlike substance, soluble in ether and alcohol. In water it swells up and forms a sort of emulsion but strictly speaking is not dissolved.

**Physiological Action.**—It has been shown by H. C. Wood, Jr., that lecithin is non-toxic, and, unless injected in enormous quantities, has practically no immediate physiological action. Amounts equivalent to 0.2 gramme per kilo somewhat slow the respiration and pulse, but do not materially alter the blood-pressure.

Lecithin is unstable and easily decomposed into its component parts, one of which, choline, is poisonous. Choline is closely related to the actively toxic substance, neurine. These poisonous principles seem to be in the nature of alkaloids. Their toxic effects consist principally in paralysis of the respiration, of the peripheral motor nerves and of the spinal cord, stimulation of the peripheral ends of the pneumogastric nerve, and temporary rise of the blood-pressure followed by a fall, which with toxic doses brings it below normal.

Danilewsky found that pups, to which were administered lecithin, increased in weight more rapidly than did the control animals, and that there was an augmentation in the number of red blood-cells without, however, a corresponding increase in the percentage of hemoglobin. Sersono obtained a similar result in studies made upon human beings, and also determined greater elimination of urea, despite which fact there was a gain in weight. This increase in the weight is probably attributable, as Sersono points out, to a stimulation in cellular reproduction brought about through the excess of protoplasmic phosphorus in the parent cell.

**Therapeutics.**—Claude and Zaky and Gilbert and Fournier have employed lecithin in *tuberculosis*, with resulting gain in weight. Sersono finds it of some value in *chlorosis*, but less active than the iron salts. Lancereaux and Paulesco employed it in two cases of *pancreatic diabetes* with gain in weight and diminution in the amount of sugar. The dose is from 0.1–0.3 gramme (1–5 grains). It was at first used hypodermically because of the fear that it would be broken up by the digestive juices into its component parts the remedial effect of which is very doubtful. Danilewsky and Gilbert and Fournier assert, however, that it acts when given by the mouth as well as when given hypodermically, although it must be administered in larger doses.

## GELATIN.

Gelatin is an albuminoid body derived from fibrous and cartilaginous tissues. Its use in medicine depends on its power of increasing the coagulability of the blood, as was first shown by Dastre and Floresco.

**Physiological Action.**—*Absorption and Elimination.*—The original results of Dastre and Floresco were obtained from the intravenous injection of gelatin. It has been, however, since then abundantly shown that the drug is capable of acting after hypodermic injections, and it must be absorbed, therefore, from the subcutaneous tissues. Camus and Gley assert that the subcutaneous injection of gelatin can have no effect on the coagulability of the blood, because, being an undialyzable substance, it is incapable of absorption. They found experimentally that the introduction of gelatin into the peritoneal cavity did not increase the coagulability of the blood, and two hours after the injection a large portion of the gelatin solution still

remained in the peritoneal cavity. Lancereaux and Paulesco deny the correctness of the conclusions of Camus and Gley, claiming that subcutaneous injection of gelatin is equivalent to injecting it directly into the lymph channels, whence it may be taken up whether dialyzable or not, pointing out as analogous the fact that ascitic fluid, which is equally undialyzable, is frequently absorbed. They found, further, that the intraperitoneal injection of gelatin does increase the coagulability of the blood, and that the solution introduced disappears from the abdominal cavity.

Concerning the question of its absorption from the intestinal tract there has been considerable dispute. It is impossible that gelatin can be absorbed by mucous membranes unchanged, since being an albuminoid it is not dialyzable. Many substances, however, are capable of producing changes in the physical properties of gelatin. Thus it has been shown by the experiments of Dastre and Floresco that if maintained at a temperature of even  $110^{\circ}\text{C}$ . for a long period of time it loses the property of jellying; strong solutions of the iodides and chlorides also destroy the property of solidifying. These changes are probably similar to those which take place in the digestion of this substance. The digestion of albuminoids such as gelatin is similar to that of the true albumins; that is, the albuminoid is converted by peptic digestion first into a substance allied to the albumoses, known as gelatose, and later into a substance known as gelatin-peptone, all of these derivatives being soluble in water at ordinary temperatures. According to the experiments of H. C. Wood, Jr., these substances, arising from the digestion of gelatin, like the gelatin itself, increase distinctly the coagulability of the blood, and being dialyzable are easily absorbed. These results seem to indicate clearly that gelatin given by the mouth and being digested is capable of influencing the clotting of the blood. And despite the contrary opinions of several authors, there can be to-day little doubt but that gelatin acts when given by the stomach.

From the experiments of Dastre and Floresco it would seem probable that the gelatin introduced intravenously was eliminated largely unchanged, since these authors found that the urine of a dog so treated solidified on cooling.

It has been claimed that in its passage through the kidneys gelatin acts as a local irritant, and Freudweiller and others have asserted that in cases of hematuria it increases rather than diminishes the amount of bleeding from the kidney. On the other hand, Lutkens found that it had no deleterious action in experimental nephritis in rabbits. Schwabe, Hahn, and many other authors have found that bleeding from the kidney was cured by the drug.

That the coagulum produced by gelatin is a true clot, and not as was by some believed, a jelly, is shown by the following facts: The process of clotting takes place at the temperature of  $38^{\circ}\text{C}$ ., at which temperature gelatin will not jelly, and gelatose, which does not jelly at all, causes the blood to clot in about one-third the normal



time. Further, it was found by Dastre and Floresco that apparently the gelatin does not enter into the composition of the clot, since the serum which is expressed from the clot is capable of solidifying on cooling, showing that at least it contains a considerable proportion of the injected gelatin.

There has been considerable discussion as to the cause of this increase in the coagulability of the blood. Zibell believes that it is due to the contained lime. This, however, seems extremely improbable, for according to his own experiments the proportion of lime present is only six-tenths of one per cent., and one gramme of gelatin representing only 0.006 gramme of lime is capable of distinctly increasing the rapidity of coagulation. Dastre and Floresco assert, moreover, that gelatin is not capable of overcoming the delayed coagulation produced by decalcification of the oxalic acid, but that it is capable of overcoming the anti-coagulant effect of peptone. Edsall believes that the increase in the rate of clotting depends upon the more rapid destruction of the red blood-corpuscles. Moll claims to have shown that gelatin increases the fibrinogen and has an agglutinating effect on the red corpuscles.

In discussions concerning the cause of the gelatin clot, investigators have curiously overlooked a fact known for a long time, namely, that gelatin is not alone in its effect upon the coagulability of the blood. Various albuminoid bodies likewise accelerate coagulation.

**Therapeutics.**—Gelatin has been employed in nearly all forms of bleeding, whether internal or external; thus, for example, in *epistaxis*, *hematemesis*, and other local hemorrhages its topical application is valuable. Internally it has given good results in *hemoptysis*, *hematuria*, *purpura hemorrhagica*, *hemophilia*, and the like. Kehr has found it useful for staunching the hemorrhage following operations on the biliary system. Lemoine has found it useful to check the bleeding following leech-bites. Manicotide and Christodulo, and Bertimo-Besdetnoff, recommend its use as a local application to the uterus in *menorrhagia*, *metrorrhagia*, and other uterine hemorrhages.

Gelatin has also been employed in the treatment of inoperable *aneurism*, and appears to be of value when the aneurism is sacculated (see Lancereaux.)

**Administration.**—The intravenous injection of gelatin, we believe, is absolutely unjustifiable, on account of the very imminent danger of the formation of thrombi. In cases where an immediate action is not necessary, we believe that the administration of gelatin by the mouth is the best method, since it avoids the danger of infection, allows of frequently repeated doses, and is probably equally efficient. We have seen hemoptysis and long-standing menorrhagia controlled immediately by the use of gelatin by the mouth. Rocchi recommends the administration of gelatin through the rectum. The dose we have employed by the mouth represents from one to four drachms of the dry gelatin three or four times daily. This may be given preferably in the form of a ten-per-cent. jelly, which may be flavored to taste. It must be remembered in this connection that the ordinary gelatin as prepared for culinary purposes contains

only three or four per cent. of gelatin itself, and must be used in correspondingly large quantities to have any effect.

In those cases of severe hemorrhage where immediate control of the bleeding is necessary and where local application is not practicable, recourse may be had to the hypodermic administration. Under these circumstances the gelatin should be given in warm solutions of from two to five per cent. in normal saline, of which from one hundred to two hundred c.c. (3-6 fluidounces) may be given at a dose. The technic for these injections is precisely the same as that employed for hypodermoclysis. Great care must be taken in the preparation of these solutions, as in a large number of cases not only pyogenic infection but fatally ending tetanus have been reported from the hypodermic use of gelatin. According to Dörfler even repeated boiling does not render the solution absolutely free from danger, since even if bacteria are killed certain toxins may not be destroyed. The patient may thus die of tetanus, although no germs are introduced. For hypodermic administration there have been placed upon the market sterilized solutions of gelatin, which are tested upon guinea-pigs and guaranteed to be sterile and free from toxin. These solutions are preferable, but should be sterilized by boiling for twenty minutes immediately before using. The prolonged boiling does not change the coagulating effect of the drug on the blood. Locally gelatin may be applied by means of a tampon saturated with hot ten-per-cent. solution. The glycerinated gelatin (*GELATINUM GLYCERINATUM*), occurs in pieces and contains about fifty per cent. of gelatin.

**NUCLEIN.**—An organic remedy whose value is very problematical is the so-called *nuclein*. Originally the term nuclein was applied to a peculiar phosphorized substance isolated from the nuclei of pus-cells. Later clinical research has shown that there are in nature numerous closely allied, phosphorized, proteid-like bodies to which the name may be applied, and which have been shown by Kossel and his co-workers to be a combination of nucleic or nucleinic acid with a proteid body. Nuclein on a large scale is preferably prepared from the yeast-cell, and readily yields *nucleic acid*, an amorphous white powder of strong acid reaction, readily soluble in alkalized water, containing as much as nine per cent. of phosphorus, but, according to Chittenden, no proteid matter. It occasionally exists free in animal cells as in spermatozoids, but is generally united with a proteid. Nuclein is furnished to commerce especially in the form of a five-per-cent. solution, of which the dose is from ten to sixty minims hypodermically. It is alleged that it is a powerful germicide, and so slightly toxic that it has been injected intravenously by Vaughan and McClintock until the blood of the animal contained one and one-eighth per cent. of pure nucleic acid without serious results. It has been especially commended in the treatment of *tuberculosis*, *puerperal fever*, and other germ diseases.

**THYROID BODY.**

The exact function of the thyroid body is not definitely known; the removal of it causes death in both dog and man. In the dog the lethal result takes place in the midst of tetanoid symptoms, death occurring usually during a convulsion. In man its absence, congenital or operative, produces the disease known as *myxædema*, first described by Ord. The symptoms of this disease are increasing weakness associated with swelling of the body, enlargement and thickening of the skin, mucoid exudation into the subcellular tissue, and a very extraordinary slowing of all functions. The appetite is feeble, the movements are slow, the temperature is subnormal, and the patient thinks with great slowness; as the days go on the universal slowing of function becomes more and more marked until the subject sinks into a condition of complete apathy with very much lowered temperature and a failure of all vital activities.

Baumann isolated from the thyroid gland a proteid substance containing iodine, which he asserted to be the active principle of the body. The activities of this substance, which is variously known as *thyroidin* or *iodothylin*, have been called in question by Gottlieb and Wormser, who state that it is incapable of stopping the progress of symptoms caused by thyroidectomy. But the contrary results achieved by E. Roos, Arthur Hennig, Truebel, Ewall, E. Levy Hildebrandt, and Baumann and Goldmann, seem to confirm the claims of Baumann; and even if the substance be not the sole active principle of the gland, much therapeutic virtue must be conceded to it. *Thyreointoxin*, which was described by Fränkel, contains no iodine, and appears not to be active (Roos); a statement which is also true of the principle separated by Dreschschel. (See Robert Hutchinson.) It would appear probable from the various researches that iodothylin is the chief active principle of the thyroid body, but that there is also in the gland a second substance which has physiological activity.

**Physiological Action.**—In elaborate experiments of G. Ballet and E. Enriquez upon dogs it was found that half an hour to two hours after the ingestion of a full meal of the sheep's thyroid there was usually elevation of temperature, with great increase of the pulse-rate, though in some cases the tachycardia alone developed. Rarely there were general excitement with paroxysms of violent tremblings and dyspnœa. The subcutaneous injection of the extract of the thyroid caused immediate fever, tachycardia, crises of trembling and dyspnœa, extreme agitation, and in two cases distinct exophthalmos. Continuous thyroid-feeding produced conjunctivitis, general wasting, and derangement of the digestion, but in no case death. On the other hand, repeated hypodermic injections of the extract led to rapid emaciation, paroxysms of violent diarrhœa and melanemia, sometimes polyuria, sometimes albuminuria, with great weakness of the hind legs, occasionally amounting to paralysis, followed by torpor, collapse, and death. Tumefaction of the thyroid



lobes was noted in some cases during life, and after death the thyroid body was found to be greatly enlarged and mottled with ecchymoses. By microscopic examination there were revealed marked evidences of inflammatory change in the thyroid gland, with destruction of the alveolar and epithelial cells and the development of sclerotic tissue.

In man *thyroidismus*, so called, has been developed in a number of cases by the excessive administration of the gland. The chief symptoms are progressive loss of weight, shortness of breath, weak, rapid pulse, and general nervousness.

As the result of his own experiments, Hertoghe asserts that the thyroid extract lessens the activity of the pelvic organs of women, while it stimulates the thoracic genital organs, so that it causes arrest of menstruation but increases the secretion of milk.

According to Ott, the drug depresses reflex action in the frog.

*Circulation.*—Vamossy and Vas state that the intravenous injection of iodothylin has no effect on pulse-rate, blood-pressure, or respiration, and attribute the symptoms seen after its ingestion entirely to disturbances of metabolism. But Haskovec, Oliver and Schäfer, and Ott agree that the thyroid extract causes a slight fall of pressure, with some increase in pulse-rate. According to Haskovec the fall of the pressure is due to depression of the heart muscle, while the increased pulse-rate is brought about by accelerator stimulation.\*

*Respiration.*—Ott found the respiratory rate increased in the rabbit by iodothylin.

*Blood.*—According to Vamossy and Vas, and Bell, the thyroid extract has practically no effect on the red blood-corpuscles or hemoglobin. M. L. Perry found, as the result of thyroid-feeding in the insane, no change in the number of the white blood-corpuscles, but a marked lessening of the percentage of the multinuclear and a corresponding increase of the mononuclear leucocytes, results which agree substantially with those of Mosely, save that the latter found some lessening in the total number of white corpuscles. Bell and Vamossy and Vas, on the other hand, found an increase in the number of leucocytes brought about by the thyroid body.

*Nutrition.*—Although Scholz, Richter, and Paul Mayer, failed to get evidences of increased nitrogenous elimination over intake, nevertheless, the concordant results of Roos, Gluzinski and Limberger, David, Schöndorff, Napier, Mendel, Ord, and others, leave no room for doubt that there is an increase in the destruction of proteid substances brought about by the continued administration of the thyroid. Roos found that there is not only an increase in the excretion of nitrogen but also in phosphorus and chlorides. Irsai, Vas and Gara have shown that these facts hold true in goitrous, and Vermehren in myxœdematous, subjects.

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\* The claim of Cyon (*A. G. P.*, 1898, 77, 42) that iodothylin will restore tone to an atropinized vagus has been disproven by Femgvesy (*W. K. W.*, 1900, xiii, 125.)

But the loss of weight is not entirely due to the destruction of albuminous tissues. Thus, in Schöndorff's experiments, out of 2.2 kilos lost in a three weeks' experiment, there was only sufficient increase of nitrogen excreted to account for one kilo of bodily tissues. Bleibtreu and Vendelstadt attribute only one-sixth of the weight-loss to the breaking down of the proteids. The conclusion seems, therefore, inevitable that there must be under the influence of thyroid-feeding not only increased katabolism of proteid, but also of fatty tissues. This conclusion is confirmed by the results of Magnus-Levy, who found an increase in the absorption of oxygen and giving off of CO<sub>2</sub> brought about by thyroiodin. In myxœdematous subjects the increase in the demand for oxygen may amount to ninety per cent. Magnus-Levy found Fränkel's thyreoantitoxin to be without effect on the exchange of gases. Schöndorff states that the destruction of nitrogenous tissues does not begin until the store of reserve fat is exhausted.

Bettmann and W. D. James report *glycosuria* following free use of the thyroid extract. Porges has found in the dog that the excretion of sugar may persist for weeks after the withdrawal of the thyroid.

**Therapeutics.**—It is evident that a myxœdematous condition of the body is the result of the absence from the blood of some principle or principles which are supplied in the normal animals by the thyroid gland, and which may be furnished to the blood by feeding with thyroid glands. It is further apparent that the myxœdematous patient who has been relieved by such artificial supply must relapse when the supply is cut off; so that treatment of a *myxœdema* consists of two stages; first, that in which large amounts of the gland are administered in order to remove the results which have been produced by the lack of the thyroid principle; second, the protracted stage of convalescence in which small doses of the gland are given continuously in order to prevent the recurrence of the myxœdemic symptoms. The most striking results are seen in *cretinism* or congenital myxœdema. In these a few months treatment with thyroid gland may convert a misshapen imbecile into a well-formed child of normal intellect.

The destruction of fatty tissues under its use would seem to render the drug of great value in *obesity*. Unfortunately, however, the system soon becomes accustomed to it, and although there is nearly always temporary benefit in properly selected cases of obesity, the patients are very liable to relapse, even despite the continued use of the drug.\*

The diseases in which the thyroid body has been given include nearly all the chronic and many of the acute troubles known to humanity. In some of them it has seemed to be of benefit, but in most has proven useless.

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\* See Grawitz (*München. Med. Woch.*, 1896, 43, 312), Mathieu (*Gaz. de Hôp.*, Paris, 1896, 69), and Yorke Davies (*Brit. Med. Journ.*, 1894, ii. 42.)

In various forms of *skin disease*, especially *psoriasis* (Bergmann), it has been recommended. It has even been asserted to be of value in *lupus* (Gould).

In mental disturbances, such as *melancholia* or *idiocy*, not dependent on myxœdema, it may be tried, although the reported results (Bell, Dobrowsky) are not brilliant, and our own trials have been an unbroken series of failures.

The recorded trials of it by Hertoghe and by Mosely in uterine troubles indicate that it may prove of service in *menorrhagia*, *endometritis*, and kindred disorders. Diaballa and Illyés report its use in a case of *nephritis* with increase of the quantity of urine and urea and diminution of the amount of albumin.

Very interesting is the report of R. Lépine of a case of progressive *myopathy*, in which muscles not very badly involved so improved that the patient, who had taken sixty grammes a week of the fresh gland, returned to his work, refusing to stay longer in the hospital. Murray has found it useful in *ununited fractures*.

In *simple goitre*,—the goitre of Switzerland,—before calcareous degeneration has taken place, thyroid treatment will often cause destruction and absorption of the overgrown gland. The extract has been used by J. William White with asserted excellent results in bringing about the absorption of large contracting cicatricial masses which resembled true *keloid*. It has been employed in old syphilitic and other *leg ulcers*, and may be cautiously tried in almost all forms of disturbed nutrition not attended by a tendency to emaciation.

In any case the occurrence of symptoms of thyroidism should be the signal for the lessening or withdrawal of the dose. In *exophthalmic goitre* the extract is *a priori* contraindicated, the most probable explanation of the symptoms of the disease being an excess of the thyroid principles in the system, and in several cases in which we have tried it it has very distinctly aggravated the symptoms. It would also seem to be contraindicated in *diabetes mellitus*.

**Administration.**—The thyroid gland may be given raw or very slightly boiled, to the amount of a quarter to half of the gland of the sheep daily. The glycerin extract or the dried and powdered gland is, however, thoroughly efficient and usually preferable. A grain of the dried gland (*GLANDULÆ THYROIDÆ SICCÆ*,) may in the beginning of the treatment be exhibited three times a day, the dose being increased until fifteen or twenty grains (1-1.3 Gm.) a day are taken, or some nervousness, shortness of breath, rapid pulse, or other physiological symptoms are produced. The dose of iodothylin is about the same as that of the dried gland (fifteen grains).

**PITUITARY BODY.**—We have very little knowledge of the physiological value of the hypophysis and almost none of its therapeutic value. Its extract causes a marked rise of pressure, which Oliver and Schäfer attribute to a contraction of the arterioles, and slowing of the pulse, which, according to Cyon, is not prevented either by



section of the vagi or by atropine. Several investigators have failed to find pharmacological activity in the hypophysis cerebri. The explanation of this discrepancy is offered by the discovery of Howell, that the pituitary gland proper is destitute of active properties, the stimulant principle residing solely in the infundibular body sometimes known as the posterior lobe of the hypophysis. Schiff has found that the pituitary body causes an increased elimination of phosphates without corresponding increase of the nitrogenous elements.

We know of no condition in which the pituitary body is of therapeutic use. Mairet and Bosc have tried it in *epilepsy*, but with no benefit.

**SPLEEN.**—In a case of severe chronic exophthalmic goitre, which was under H. C. Wood's care some years ago, an acute splenitis ending in abscess developed. In the second or third week of the attack the enlarged thyroid body began to diminish, and by the fifth week had disappeared. After a protracted and extremely severe illness the woman finally recovered from the splenic abscess, and has since remained free from any symptoms of exophthalmic goitre.

In myxœdema, cretinism, etc., it is well known that the spleen is frequently enlarged, suggesting that there is some relation between this organ and the thyroid body. That the splenic extract is not inert is shown by the discovery of Oliver and Schäfer, that its intravenous injection in the dog produced a fall, followed by a marked rise, in the arterial pressure.

We have used the splenic extract in various cases of *exophthalmic goitre*, and have found that two practical difficulties attend its administration. If it be given by the mouth in sufficiently large doses to produce distinct effect it is very apt to cause nausea and sick stomach. If it be given hypodermically it frequently causes local abscesses. The few trials we have made of it indicate that it is at least worthy of being essayed in this intractable disorder. Clark has found the extract of spleen useful in cases of *insanity* dependent on physical exhaustion, as in *puerperal weakness* or *anemia*.

### ANTITOXINS.

As a result of growth of pathogenic bacteria in the animal system there are produced two substances known as toxins and antitoxins. A toxin is a substance produced by the bacterial growth which is harmful to the host and generally speaking, therefore, favors the growth of the bacteria. The antitoxin is a substance which tends to restrict the growth of the bacteria or to neutralize the harmful effects of their growth. It appears to be the defensive reaction of the system against the bacteria. The therapeutic uses of toxins are considered in the article on opsonins (p. 414).

The mode of action of the antitoxin in infectious diseases has been the subject of a large amount of surmise and study, but while a number of interesting theories have been suggested, notably that of Ehr-

lich, it must be confessed that we have no positive knowledge of the manner in which this substance acts in infectious diseases. It seems probable that the actions of different serums are not the same. If antitoxin be given to an animal suffering from an infectious disease due to local lodgement of a pathogenic germ, the first evidence of beneficial action is failure of the germs to grow, though they are not killed.

**ANTIDIPHThERIC SERUM.** (*Serum Antidiphthericum*), *Diphtheria Antitoxin*.—The U. S. Pharmacopœia requires that the antidiphtheric serum shall be of the standard strength, expressed in units of antitoxic power, established by the U. S. Public Health and Marine Hospital Service, and it should always be freshly prepared, as even when preserved in the best manner it gradually loses its power, the annual loss varying from ten to thirty per cent. Although the abundant clinical evidence appears to demonstrate beyond all doubt that diphtheria antitoxin is an absolute specific in diphtheria, it is essential that it be used early, as it acts chiefly by arresting the growth of the bacilli. If the antitoxin be given late in the disorder it may arrest the further growth of the germ, but the patient may die, nevertheless, because the tissues are already fatally poisoned with the toxin, or, perchance, have already undergone an irreparable degeneration. Again, there is in every bad case of diphtheria after the first twenty-four hours a general septic infection: so soon as lodgment has been fairly effected by the Löffler bacillus, and local tissue-change set in, streptococci and other septic germs begin to develop rapidly in the dying tissues, and very soon give origin to a general septic infection, which is most fatal cases of diphtheria is an important factor in the causation of death. Evidently a Löffler bacillus antitoxin is useless against a streptococcus toxin.

The absolute importance of the early use of the antitoxin during diphtheria is very evident. There are very few, if any, well-observed cases of diphtheria on record in which it has been positively determined that the antitoxin, administered during the first few hours after the outbreak of the disease, has failed to bring about a cure. On the other hand, statistics seem to show that if the injection be postponed to the fifth day, the mortality-rate is not reduced by the use of antitoxin. Our modern municipal scientific methods, notwithstanding all their laudations, are liable to become causes of death. A case of suspected diphtheria presents itself to the practitioner; already the child has been sick, it may be, one or two days. A culture-tube is prepared, sent to the municipal laboratory, examined, and the result sent back to the practitioner, who then goes to see the patient. It is very fortunate if not more than one day is lost in this way, and the loss of those hours may well mean the loss of life, for the time has elapsed during which the antitoxin would best act. There is no reason at present for believing that the antitoxin used in moderate quantity does harm when the child has not diphtheria. When, therefore, any case presents the clinical aspect of diphtheria

the antitoxin should be used at once. For educational purposes, and for rendering definite our knowledge, the municipal laboratories are very useful; for purposes of treatment the less attention paid to them probably the better for the patients.

The greatest danger after that of not using diphtheria antitoxin early enough is that it be not given freely enough. The ordinary dose of diphtheria antitoxin for an adult is from two thousand to five thousand units, according to the severity of the case. In very virulent cases, however, it may be advisable to exceed this dose, since frequently when the ordinary quantity fails a dose of ten thousand to twelve thousand units proves efficacious. Since the injections are practically harmless, it seems better to err on the side of too large than too small dosage, although Musser has recommended the use of comparatively small doses of five hundred to one thousand units repeated at frequent intervals every six hours. It is affirmed that the milder method is less likely to be followed by disagreeable antitoxin symptoms; but as these disagreeable symptoms are of little importance, the superior promptness and certainty and the avoidance of frequent disturbance of the patient, which attend the more heroic method, seem to us to make it preferable.

The dose of antitoxin for children should be proportionately much larger than in adults, and the American Pediatric Society recommends that in children over two years of age, in cases of moderate severity, from fifteen hundred to two thousand units should form the initial dose; in children under two years, quantities up to one thousand units may be given.

Antidiphtheric serum is also serviceable as a prophylactic in well persons who have been exposed to the infection. In this case the dose should be from 500 to 1000 units.

The use of antitoxin in any case of diphtheria should not interfere with the usual local and general treatment.

The antitoxin solution should be injected deeply into the buttocks or back with every possible antiseptic precaution.

In most cases the injection of the antitoxin is followed in a very few hours by a fall of temperature and a decrease of the local diphtheritic symptoms. Occasionally, but not usually, this amelioration is preceded by a temporary rise of temperature. Sometimes the disagreeable symptoms produced by the injection appear in a few hours; perhaps more commonly they are not developed until from six to nine days; and it is even affirmed that they may be delayed to nine weeks, and that they have led to the mistaken diagnosis of scarlet fever or other exanthema. The characteristic symptoms are rise of temperature, with eruption upon the skin, and rarely swelling and pain in the joints. The skin eruption may be purely erythematous, is often scarlatinoid, and perhaps as frequently rubeoloid, and sometimes it takes the form of a severe urticaria.

The unpleasant effects which follow the injection of diphtheria antitoxin seem to be due rather to the introduction of the foreign



serum into the blood, than to the antitoxin itself. The attempt has been made to prepare an antitoxin which shall be free from these poisonous albuminous bodies. The methods employed are based upon the fact that the antitoxin is in the nature of a globulin and is precipitated from the blood serum by a saturated solution of ammonium sulphate, while most of the albuminous bodies in the blood serum are not. (See Park and Throne.)

*Tetanus.*—Despite the vigorous claims of various scientific authorities concerning the value of tetanus antitoxin, the results with this method of treatment have not been very brilliant. Goodrich, in a collection of two hundred and twenty-six reported cases, found that sixty-four per cent. of those treated by other methods recovered, and only sixty-three per cent. of those treated by antitoxin. The published mortality of other authors who have employed tetanus antitoxin varies from thirty-five to sixty per cent.

In the laboratory, tetanus in the lower animals can be cured with almost absolute certainty by the proper use of antitoxin. The causes of the discrepancy between laboratory and practical results have been pointed out by Tsuzuki. This author found that tetanus antitoxin was capable of saving mice only when the dose of the toxin was not more than two or three times the minimum fatal dose, and when the antitoxin was injected within six hours after the administration of the toxin. He further found that the antitoxin had much more effect if injected in the neighborhood of the inoculation with the toxin than when administered subcutaneously in another part of the body.

It is very evident from these results that, in cases of human tetanus, where the virulence of the infection is unknown and where there is usually a considerable amount of toxin in the system before the outbreak of the symptoms, tetanus antitoxin cannot be expected to rank as an infallible cure for this disease. Nevertheless, especially in those cases which are seen early, the immediate use of antitoxin, since it need not interfere with other methods of treatment, appears to be advisable. There is also much evidence of its value as a prophylactic.

The United States Marine Hospital Service has established a unit for antitetanic serum which is compulsory for American makers of serum. The dose is from 2000 to 5000 of these units.

*Streptococcus Infections.*—The streptococcus antitoxin has been recommended in the treatment of *erysipelas*, *puerperal septicemia*, and similar conditions. The reports of the results, however, do not seem to be very encouraging. In three hundred and fifty cases collected by the American Gynecological Society, the mortality in puerperal sepsis treated with streptococcus antitoxin was thirty-three per cent., which is no less than the ordinary mortality rate in these cases. It is evident that a streptococcus antitoxin can prove of no value in staphylococcus infections. Streptococcus antitoxin has also been used in the treatment of secondary infections with the streptococcus

occurring in *diphtheria* and *scarlet fever*. There is no generally recognized unit of streptococcus antitoxin, and therefore cannot be any definite dosage; so that the practitioner can only follow the directions given with the antitoxin serum by the manufacturing firm.

*Cholera*.—Lazarus discovered that the blood-serum of human beings who have recovered from an attack of Asiatic cholera possesses properties which render it capable of protecting animals from fatal doses of the spirillum of Asiatic cholera. He regarded this substance as being of the nature of an antitoxin, and the protective action of the human serum as similar to the antitoxin of diphtheria, tetanus, etc. The studies of R. Pfeiffer, however, have shown that the principle contained within the blood-serum is not of the nature of an antitoxin, but is bactericidal; it acts by causing rapid disintegration of the introduced cholera organism, and thus prevents the rapid multiplication that brings about the death of the exposed animal. A few minutes after the simultaneous introduction of the cholera vibrio and of the blood-serum into the peritoneal cavity of small animals, such as the guinea-pigs, the micro-organisms begin to disintegrate, and very soon they are completely destroyed.

Pfeiffer also showed that dead cholera organisms are still toxic and capable of acting similarly to the living germs. Haffkine has originated a method for the immunization of human beings against cholera; he cultivates the germ in bouillon, and after a certain growth has been obtained, heats sufficiently to kill the germ without completely destroying the cholera poison which adheres to its body, and which is a very sensitive substance. Injections of such cultures in human beings are followed by a local reaction and febrile movements and the appearance of a protective substance in the blood-serum in man similar to that present after an attack of the disease. Two injections are commonly made at the interval of about a week, after which the protection of the individual is believed to be complete. This method has been applied on a large scale in India, and apparently with a measure of success.

*Hay-Fever*.—Dunbar's Hay Fever Antitoxin is at present obtained by inoculating healthy horses with a toxin obtained from the pollen of certain flowering grasses and plants. Dunbar in 1903 isolated from the pollen an active toxin the exact nature of which he could not determine further than saying it was a toxalbumin. Hay-fever patients showed a marked reaction to this toxin, at any time of the year, if it was brought in contact with the mucous membrane or injected subcutaneously and these attacks were instantly relieved by the application of the antitoxin.

When Dunbar's antitoxin was first used in America, the reported results by Mayer, McCoy and others were so favorable that the use of the treatment rapidly spread. In the year 1904, the results obtained were not so favorable and the use of the antitoxin rapidly sank in popularity. This difference in results is probably dependant on the difference between European hay-fever which occurs in the

early summer and the American type which occurs in the late Summer or early Fall. The first cases in this country were treated by an antitoxin especially prepared by Dunbar and his assistants from ragweed pollen and sent to a few well-known specialists. In the summer of 1904 the product obtained was that produced by Schimmell & Co., from flowering grasses and was used promiscuously without attention to detail. From the results of 1903 and 1904, it seems that in America, the antitoxin to be of any value must be prepared from the pollen of goldenrod, ragweed or one of the toxic plants which bloom late in the summer. In exceptional cases of mild hay-fever, frequently called rose cold, the antitoxin prepared from the grasses is more efficient. The results of the summer of 1905 confirm this assumption and since the antitoxin prepared by Schimmell & Company was put on the market and more attention given to the treatment in details, the results were very favorable.

The present status of the antitoxin treatment of hay-fever is that in the majority of cases of true hay-fever in which the attack begins about the second week in August, the careful use of the antitoxin will give more or less benefit. To obtain the greatest relief the treatment should begin 4 or 5 days before the expected attack and keep up regularly throughout the whole hay-fever season. References to the literature may be found in the article of H. W. Loeb.

*Bubonic Plague.—Pest.*—The discovery by Yersin, in 1894, of the bacillus of the bubonic plague has caused protective measures to be employed in combating that disease. Several methods are now in use; that of Yersin consists in the immunization of horses or other large animals to injections of the plague bacillus, and the use of the blood-serum obtained from these animals in a manner similar to the employment of the antitoxin of diphtheria.

Haffkine's method, which has been used on a larger scale, and apparently with less doubtful results than that of Yersin, is in principle similar to the protective inoculation for cholera. Bouillon cultures of the plague bacillus (the organisms being obtained directly from human cases of the plague) are incubated for about two weeks. The bouillon is finally heated to 60° C., for about twenty minutes, in order to kill the bacillus, after which half of one per cent. of phenol is added in order to preserve the serum from accidental contamination by micro-organisms. The injections are made into the soft tissues of the thigh, the entire culture being used. Two injections are usually employed, at intervals of six days. The symptoms are elevation of temperature and swelling about the point of inoculation, most marked after the first injection. The second inoculation is believed to give protection. The statistics gathered from India, where the plague has prevailed, are highly encouraging as to the value of this procedure. The serum is of no use in the treatment of developed cases of the plague.

Another method of protection which is being employed is that of Lustig, who produces from the dead plague bacillus, by treatment



with acids and then alkalies, a nucleo-proteid, whose inoculation into animals and human beings gives active immunity to the plague organism. The blood-serum from animals so immunized may be used in the treatment of the developed plague; or, injected into healthy human beings, affords a passive immunity which, however, endures only a few weeks. It is, therefore, capable of use in protecting for a short time a community exposed to the plague, although less reliable than Haffkine's serum. Its advantage is that it affords immediate protection, whereas the other means employed require a number of doses before the protective action appears.

The blood-serum of human beings and animals who have withstood injections of the plague bacillus possesses agglutinating properties for the plague organisms; this agglutination, however, does not appear early in the infection, but is a phenomenon of convalescence. Its usefulness, therefore, in the diagnosis of plague is doubtful.

*Snake-poisoning.*—Swall appears to have been the first to demonstrate the possibility of producing immunization against the venom of serpents, having proved as long ago as 1887 that it was possible by a series of inoculations of increasing intensity temporarily to immunize pigeons against the rattlesnake-poison.

The serum of the blood of the artificially immunized animal has been found to be of remedial value in snake-poisoning, and has been put upon the market commercially. Its use as a prophylactic is justifiable only in certain conditions when there is about to be an extraordinary exposure to a possible snake-bite, since the immunity it confers lasts only for a short time. The value of the serum as a curative agent has, however, been proven not only in the laboratory but also in a number of recorded cases of snake-bite; so that it should be carried by those whose duties or desires lead them into tropical countries where poisonous serpents abound.

Antitoxin for snake-venom, suggested almost simultaneously by Phisalix and Bertrand, and Calmette, was first practically prepared by Calmette. As was originally shown by Mitchell and Reichert, snake-venom contains two toxic substances—a local and a constitutional poison. The serum of Calmette is prepared from cobra-venom, which contains comparatively little of the local irritant, and, according to McFarland, immunizes only against the generally acting element of snake-venoms. Poisons of the American snakes, such as the rattlesnake, the moccasin, etc., are mostly highly irritating venenes. In an effort to produce an antitoxin which would be efficacious against these serpents, McFarland was unsuccessful in producing an immunity in the horse to the local irritant action of the poison, although he obtained a serum which overcame the constitutional effect of these venoms. Although Calmette claims that his antitoxin is efficacious not only against various serpent-poisons, but against scorpion-bites, McFarland has shown that although it destroys the nerve-depressant poison it does not overcome the effects of a great local irritation which is caused by such venoms as rattlesnake-poisoning, and is not a sure life-saving remedy. More recently Noguchi has succeeded in obtaining a rattlesnake antivenin. Fraser asserts, however, that the dose of antivenin required to afford an efficient degree of immunity is so large as to make it impracticable in human poisoning. He claims that 350 C.c. are necessary to cure a man of one hundred and seventy pounds weight; the ordinary quantity recommended is 15 to 20 C.c.

As the result of experiments by various observers, it has been established that venomous serpents are poisoned by snake-venom only with the greatest difficulty; that the ordinary non-poisonous snakes share this immunity to a distinctly less degree; and that certain of the higher animals, notably the mongoose, are distinctly resistant to the poison. It is probable that the immunity in the higher animals is an inherited, "acquired character," due to the repeated survival of generations of bitten animals, the immunity of the individual being partially transmitted to the offspring.

According to the reports of missionaries, the various compounds prepared by the "witches" in Africa for the cure of snake-bite have the liver of the serpent in their combination; and T. R. Fraser, of Edinburgh, has experimentally proved that the bile of poisonous serpents is a very active antidote to the poison, neutralizing the venom when mixed with it in equal quantities. Even the bile of ordinary snakes has a feeble antidotal power. When after a bite it is possible to kill the snake, all of its bile should be injected into the immediate neighborhood of the wound.

### OPSONINS.

In 1903 Sir Almooth Wright announced the discovery that for phagocytosis to take place there was necessary certain constituents in the blood serum which he assumed acted upon the bacteria to prepare them for leucocytic destruction. These bodies, the nature of which is not yet definitely proven, were by him called opsonins. Wright and his followers have further shown that in certain conditions the amount of opsonin in the blood may become markedly reduced so that phagocytosis takes place much less actively and the body becomes correspondingly more susceptible to bacterial invasion. The figures indicating the power of the blood serum to render bacteria destructible by leucocytes in comparison to the activity of normal serum, is known as the opsonic index. The opsonic index may frequently be greatly increased by various appropriate measures, one of the most potent of which is the presence of bacterial toxins in the blood.

From these observations there has arisen in the last few years a new method of treating infectious diseases by injection of emulsions of dead bacteria. It is perhaps hardly accurate to speak of this method as new as it has been employed for many years in the treatment of tuberculosis and is very similar to that employed by Haffkin as a protection against cholera. (See page 411.)

As pointed out by Ross there are three classes of cases of bacterial infections presenting low opsonic indices. The first of these comprises local infections in which the bacterial products have not entered the general circulation and there is, therefore, lacking the reactive stimulation of the general system. The second group comprises cases in which the bacterial invasion of the general system is so great

as to apparently overwhelm the opsonogenic powers of the system. The third class of cases includes those of such low vitality that they are not able to react to the stimulant influence of the toxins. Manifestly it is only in the first group of cases that the treatment of bacterial inoculations can be expected to give beneficial results.

This group of cases includes first, a large number of bacterial skin diseases, as, *furunculosis*, *acne*, *sycosis*, and the like. Secondly, localized infections by pyogenic organisms, as *carbuncles*, *boils* and walled *abscesses*. And finally, early cases of *pulmonary tuberculosis* in which the disease assumes a local infection of the lungs rather than a systemic morbid process. The treatment of tuberculosis by means of the toxins of the tubercle bacilli was introduced by Koch many years ago. His method was later modified so that instead of the toxin the bacteria themselves previously devitalized by heating were injected. The method has been commended by various clinical authorities, notably Von Ruck, but has become especially popular since the explanation of the *modus operandi* was offered by Wright's opsonic theory. While the results from the injection of tuberculin have not been so brilliant as opsonic therapy in some other infections yet the trend of evidence to-day is that it possesses distinct value in certain cases, especially in the early stages.\*

Apparently the opsonins are specific, that is, for each different variety of bacteria there is necessary for phagocytosis to occur, the presence of a definite element in the blood so that the opsonic index may be very high for one organism and low for another. While it is impossible in a work of this character to go into the detailed description of the opsonic therapeutic method, we will briefly mention the general principles involved. It is first necessary to determine the opsonic index of the patient for the infection from which he is suffering. For this purpose the micro-organism which is the cause of the trouble is cultivated on an ordinary media and an emulsion of definite strength is made. The patient's serum is obtained from a blood clot and added to a mixture of washed leucocytes and bacteria, and the number of bacteria found within the leucocytes counted. A similar operation is performed using serum of a healthy individual with all other conditions precisely similar, and the figures compared. A culture is then made of the bacteria and heated to a temperature of 60° to 70° C. (140° to 150° F.) to kill the bacteria, and doses of several million dead bacteria injected subcutaneously. It is generally preferable to employ cultures made from bacteria obtained directly from the patient, although if the species of bacteria is definitely known the same variety obtained from other sources may be employed.

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\* Tuberculin is also largely used as a diagnostic measure by the veterinarian, and occasionally in human medicine. When tuberculin—that is, tubercular toxin—is injected into the blood in certain small quantity, it produces no febrile reaction in the normal individual because there is not enough of it present in the system. If, however, the injected toxin be added to a toxin which has been previously produced in the body, and which is already in the blood, the aggregate amount will be capable of producing a hectic fever, which will demonstrate the existence of a toxin-producing focus in the body,—i.e., of tuberculosis.



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## FAMILY IV.—ANTIPERIODICS.

### CINCHONA.

The trees comprising the genus *Cinchona*, of which there are many species recognized by botanists, are handsome evergreens indigenous to South America, especially along the slopes of the Andes at an altitude of from five to ten thousand feet above the level of the sea. The U. S. Pharmacopœia recognizes the *Cinchona ledgeriana*, *calisaya officinalis* and—under the name of *cinchona rubra*—the *Cinchona succirubra*, as well as various hybrids of these species.

It is uncertain, but improbable that the South American natives were acquainted with the medical properties of cinchona. The earliest record of its use appears to be in 1630, when Canizares who was then governor of Loxa, one of the divisions of Peru, was cured of ague by its use. In 1638, the Countess of Cinchon, wife of the viceroy of Peru was cured by the bark and sent a quantity of the remedy to Europe where it was employed under the various names of “countess bark,” “Peruvian bark,” etc. In the early part of the last century it became evident that owing to the reckless methods of collecting the bark that the natural source would soon be exhausted, and after various efforts to establish artificial plantations, the Dutch finally succeeded, in 1853, in starting a successful cinchona grove in the island of Java. Since then the tree has also been successfully cultivated in India and Ceylon. Of the nearly eighteen million pounds of cinchona bark produced annually, over fifteen million pounds come from the island of Java, and about seven hundred thousand pounds from South America.

The official portion of the tree is the bark, which occurs in quills or curved bits of various size, externally of a grayish color, interior brown, and with a very bitter and somewhat astringent taste.

Although the cinchona bark contains a large number of alkaloids, only four are present in sufficient proportion to be of any practical importance. They are,—*quinine*, *cinchonine*, *cinchonidine* and *quinidine*. Of these the first three are official. The bark should contain not less than five per cent. of total alkaloids.

#### Official Preparations :

Fluidextractum Cinchonæ.....	15 to 30 minims (1–2 C.c.).
Tinctura Cinchonæ (20 per cent.).....	1 to 2 fluidrachms (4–8 C.c.).
Tinctura Cinchonæ Composita (Huxham's Tincture) 10 per cent.....	1 to 2 fluidrachms (4–8 C.c.).
Quinina.....	2 to 5 grains (0.13–0.3 Gm.).
Quinina Sulphas.....	2 to 10 grains (0.13–0.6 Gm.).

**Official Preparations** (*Continued*).

Quininæ Bisulphas.....	2 to 10 grains (0.13–0.6 Gm.).
Quininæ Hydrobromidum.....	2 to 10 grains (0.13–0.6 Gm.).
Quininæ Hydrochloridum.....	2 to 10 grains (0.13–0.6 Gm.).
Quininæ Salicylas.....	2 to 10 grains (0.13–0.6 Gm.).
Cinchonidinæ Sulphas.....	3 to 15 grains (0.2–1.0 Gm.).
Cinchoninæ Sulphas.....	3 to 15 grains (0.2–1.0 Gm.).

QUININE was first distinctly separated from the other ingredients of the bark by Pelletier and Caventou in 1820.

The neutral, official *quinine sulphate* occurs in light silky crystals, soluble in seven hundred and twenty parts of cold or in thirty of boiling water, but very freely so in acidulated solutions. Therefore, when it is administered either by the subcellular tissue or by the rectum the alkaloid should be given in the form of the bisulphate and in distinctly acidulated water.

**Physiological Action.**—*Local Action.*—Quinine is distinctly irritant to the mucous membranes, but has little or no influence upon the sound skin. It was stated as long ago as 1765 by Pringle, that cinchona bark itself is distinctly antiseptic and has been confirmed by Hallier, Binz and others. More recent researches have demonstrated that quinine is actively germicidal, and that in the proportion of one part to three hundred it will preserve for a long time flesh, meal, milk, butter, urine, albumin, etc., and will check very markedly the alcoholic fermentation in honey or in syrup.

According to the experiments of Binz, the larger infusoria, such as *Paramecia* and *Colpoda*, are killed by a solution of quinine of the strength of 1 in 800 immediately, of 1 in 1000 after some minutes, of 1 in 20,000 after some hours. Upon the ordinary mould *Penicillium*, upon *Vibrios* and *Bacteria*, as well as upon the higher infusoria, quinine acts with a similar fatality. In the case of the *Vibrios* and *Bacteria* a decidedly stronger solution than the one mentioned is required to quiet movement. Bochefontaine found that a solution of one per cent. was needed for a vigorous rapid action, and that some active granules could even be found in it after three days.

The fact that fungi will appear after a time in an ordinary solution of quinine sulphate demonstrates that at least upon some of the lower organisms it has but comparatively little influence, although on others it acts with much power.

*Absorption and Elimination.*—Owing to its insolubility in simple water or alkaline solutions, quinine can enter the body with rapidity only under circumstances in which it is exposed to the solvent power of acids.

Taken into the stomach, the quinine salt is dissolved by the acid gastric juice; but if it be not absorbed at once, passing into the intestines it is liable to be precipitated by the alkaline juices and the bile salts.

Quinine is eliminated chiefly through the kidneys, escaping in large part unchanged, but probably in part undergoing alteration.\*

That a considerable portion of ingested quinine can be recovered from the feces has been proven by Kerner and other chemists. It is probable, however, that some of this fecal quinine has been absorbed and subsequently cast out by the liver as a very insoluble biliary salt, since Albertoni and Ciotto found that when they injected quinine into the jugular vein it failed to appear in the bile, although when given by the mouth it was freely eliminated with that secretion.

According to Briquet, quinine may generally be found in the urine half an hour after the administration of a large dose. Its removal, according to the researches of Binz, goes on slowly, for it is stated that in six experiments only a little more than two-thirds of the ingested quantity was excreted in the first forty-eight hours. Further, De Renzi, Yvon, and Dietl have found it in the urine six or seven days after the ingestion of the last dose. It is probable that some of the quinine is eliminated through other channels than the kidneys, since Binz had found it in the saliva of a poisoned dog, and Landerer states that he has detected it in the urine, sweat, tears, milk of nursing women, and in the serum of dropsical effusions, while Albertoni and De Renzi found it abundant in the bile when it had been taken by the mouth, but not when it had been given hypodermically. Merkel discovered that in the dog from eighty-six to eighty-eight per cent. of the quinine escaped unchanged from the kidneys, the remainder being converted into new substances. F. K. Kleine determined that 29 per cent. escaped through the urine in twenty four hours, the elimination being at its height in about six hours after the taking of the drug.

As the blood is alkaline, *a priori* it would be expected that the quinine salt would be precipitated in the blood; that this does not occur is, according to the researches of Kerner, due to the solvent power of the carbonic acid in normal blood.

The authority mentioned found that one thousand parts of blood which was defibrinated and deprived of its gases at a temperature of 36° C. dissolved in an hour only 0.398 part of pure quinine. Water saturated with carbonic acid gas dissolves the quinine sulphate pretty freely; and Kerner also experimentally determined that when a neutral solution of a salt of quinine is added to a very dilute solution of sodium carbonate no precipitate occurs. It would appear, then, that the quinine is held in solution in the blood by reason of the loosely combined carbonic acid gas in that fluid.

The question as to the rate and completeness of the elimination of quinine is one of great practical importance. It is evident that it is both absorbed and eliminated more rapidly when it is given in solution or in the form of the acid salt than when taken in pill or capsule. Under favorable circumstances, with the dose not too large, it is probable that absorption is practically complete within two hours after the taking of the quinine into the stomach, so that the maximum effect of the single dose is probably reached in from one to two hours. Thau determined that from a third to somewhat

\* G. Kerner (*Pflüger's Archiv für Physiologie*, 1870) asserts that the quinine as excreted is in an amorphous, uncrystallizable form. He also has discovered in the urine of persons taking quinine a peculiar substance, sometimes amorphous, sometimes in acicular prismatic crystals, free from bitter taste, possessing the quinine inflorescence, which he believes to be a derivative formed in the body from the ingested alkaloid. He has not been able to get this substance in such quantity as to analyze it or further examine it, but has produced a principle (*dihydroxyl-quinine*) which he believes to be identical with it by acting on quinine with the potassium permanganate. An elaborate series of experiments have shown that the dihydroxyl-quinine is physiologically inert. This dihydroxyl-quinine must be produced in small amount, if at all, as there is abundant evidence that quinine is largely excreted as quinine (see *Pharm. Journ. and Trans.*, ix. 125).



less than half of the ingested quinine escapes from the body in the first six hours, and that in the first twelve hours about three-fourths are excreted. Welitschkowski found an elimination of sixty-five per cent. the first day and twenty-five per cent. the second day. Prior gives the second day as the usual final limit of elimination. We think it more than probable that after *a few doses the alkaloid is practically eliminated in forty-eight hours*, but that when it has been given continuously, or when kidney disease or great feebleness of circulation exists, the system may contain a notable amount of the quinine for a longer period. The researches of Welitschkowski are in accord with those of Jürgensen and Thau in showing that in cardiac and renal disease and in low fevers elimination proceeds very slowly, more of the alkaloid being thrown off in the second than in the first six hours after its ingestion.

**Physiological Action.**—*Nervous System.*—In the lower animals large doses of quinine frequently cause violent epileptiform convulsions. Given to dogs in sufficient quantity, it produces restlessness, followed by muscular tremblings, which have been compared to those of paralysis agitans, loss of power deepening into more or less complete paralysis, great dyspnoea, and cerebral symptoms, such as anesthesia, blindness, stupor, or violent delirium, dilated pupils, coma, and convulsions. Death has been shown by Heubach to be produced, at least in the lower animals, by a failure of the respiration. The cause of the convulsions in the lower animals is unknown. In the frog quinine lessens reflex activity probably by stimulating the spinal inhibitory mechanism (Setschenow's centre). This action may explain some of the therapeutic virtues of the drug.

The experiments of Albertoni would indicate that quinine is capable of convulsing both the pigeon and dog after destruction of the cerebrum. Although in the frog it causes some temporary increase of reflex activity its stimulant action upon the cord is not sufficient to account for its convulsive action. In this connection the fact noted by Brown-Séquard, and confirmed by Albertoni, that the cinchona alkaloids increase the frequency of the seizures in epileptics, becomes of great interest. When given to the frog in large doses quinine lessens the reflex action apparently by the effect upon the spinal inhibitory mechanism, although in toxic quantities it also has a direct depressant action upon the motor cord. Jakoubowich has noted the epileptiform convulsions in dogs from quinine and it has been produced by cinchonidine in various animals. Chirone and Curci found that in the pigeon this action of cinchonidine is prevented by ablation of the cerebral hemispheres, but Albertoni objects with much force that these observers gave the pigeon the alkaloid too soon after the ablation, while it was still profoundly affected by the shock and hemorrhage of the operation. Albertoni found that, if the pigeon is allowed to recover, the cinchonidine is capable of causing convulsions; also that in dogs with the motor zone of the cerebral cortex destroyed, the alkaloid causes epileptiform attacks, and that therapeutic doses do not increase the excitability of the cerebral cortex in the dog.

Louis Dupuis found that reflex action may be normal in poisoned dogs and rabbits, although there is complete loss of sensibility: if this be correct, the toxic dose of quinine must paralyze the perceptive centres in the cerebrum.

According to the experiments of Briquet, a solution of quinine sulphate injected into the carotid will in some cases produce meningitis. In doing this, it is evident

that the salt acts as an irritant to the membranes of the brain rather than as a nervous stimulant: indeed, experimental evidence proving that quinine is a cerebral stimulant seems to us to be wanting.

Schlockow was the first to notice a stage of increased reflex activity produced in the frog by quinine; its existence was subsequently denied by A. Eulenburg, but has been reaffirmed by H. Heubach and by David Cerna, who agree in finding that it occurs only after very minute doses. In his investigations made in the laboratory of the University of Pennsylvania, Cerna found that this stage of excitement is probably caused by a stimulant influence upon the peripheral sensory nerves, as it did not occur when the abdominal aorta was tied previous to the exhibition of the alkaloid. Two facts, first pointed out by T. A. Chaperon, have been so abundantly substantiated that we must accept them as established. They are, that in *small* doses quinine causes in the frog a lessening of the reflex activity, which is removed by section of the medulla, and in *large* doses it produces a permanent palsy of reflex activity. The only explanation of the first lessening of reflex activity which is at present plausible is that it is due to stimulation of Setschenow's centre.

Sedgwick combats this theory just spoken of; he believes that the inhibition of the reflexes is such as occurs when a sensitive nerve is galvanized, and is the result of a stimulation of the peripheral afferent cardiac pneumogastric nerve-endings by the quinine. He bases his theory chiefly on the fact which he has discovered, that atropine prevents the primary inhibition of reflexes by quinine. This is, however, readily explainable without the adoption of the theory of Sedgwick, and the results which he obtained after division of the pneumogastries are scarcely in accord with his theory.

The cause of the permanent influence upon reflex activity has not yet been accurately determined, but there is reason for supposing that peripheral sensory nerve-endings are first paralyzed.

Chaperon and Wild found that the motor nerve-trunks are unaffected, but this does not prove that the spinal centres are paralyzed, especially as Wild's experiments seem to show that the nerve-endings in the muscles are attacked. (See below.) A. Eulenburg asserts that voluntary movements persist after reflex actions, and that the quinized frog will turn into its normal position when laid upon its back, although ordinary reflex actions are completely abolished. This, if correct, certainly shows that it is either the sensory nerves or the receptive centres of the cord whose paralysis by quinine puts an end to ordinary reflex movements. So that, accepting the various results reached by experimenters, it is probable that in frogs quinine first excites and then paralyzes the peripheral sensitive nervous system.

*Special Senses.*—The disorders of special senses caused by quinine are due to an action upon the peripheral sense organs; an action which is probably directly exerted upon the nerve-structure involved, and is not a secondary result of changes in the circulation of the organ, although it is still believed by many authorities that the drug acts directly upon the aural and retinal circulation.

In regard to the aural action of quinine, Roosa affirms that large doses of quinine cause congestion of the blood-vessels of the middle ear, and in our own observation in persons suffering from unilateral chronic inflammation of the middle ear, small doses of quinine will produce tinnitus aurium of the diseased ear without affecting the sound ear. Again, the fact, long since pointed out by Kirchner, that in the lower animals killed with quinine, very great congestion of the middle internal ear and the labyrinth, with bloody exudation and in some cases hemorrhage, are present after death, has been abundantly confirmed; but Wittmaack, as the result of his experimental investigations, believes that these changes are not caused directly by the quinine, but are the result of the long drawn out suffocation which precedes death. Wittmaack further finds that the ganglionic cells of the cochlear ganglion are very distinctly altered by the poison, the anatomical changes being demonstrable

four hours after the taking of the fatal dose. He was also able to detect alterations in the protoplasm in these cells, as the result of chronic poisoning with quinine.

Analogy would indicate that as in the retina so also in the peripheral aural apparatus, the first effect of quinine upon the circulation is a spasm of the vessels, but at present there is no proof of this. The evidence still indicates (not demonstrates) that quinine does cause congestion of the peripheral nerve aural apparatus, but whether this is or is not preceded by a period of ischemia, and whether it is primary or secondary to the action of the drug upon the nerve-endings themselves, is undetermined.

*Muscles.*—According to the experiments of H. Kobert, very large doses of cinchonine, and probably therefore of quinine, lessen the excitability of the muscles. This is confirmed by the experiments of R. B. Wild, who finds that solution of quinine, 1 to 1000, brought in contact with the isolated muscles of the frog, diminishes the irritability of the muscle and alters to some extent its relations with stimulation. The peripheral nerve-endings appear to be more sensitive than is the muscle, for when a solution of 1 to 4000 was employed, galvanization of the nerve failed to elicit a response, although the muscle contracted when the current was applied to it directly.

*Abdominal Organs.*—Upon the stomach and intestines quinine acts very much as does a simple bitter. In moderate doses it stimulates digestion and increases the appetite; in large doses it not infrequently causes nausea and vomiting. When there is any morbid irritability of the mucous membrane of the stomach or bowels, its irritant action is often very marked, and its continued use in large doses has been known to cause gastritis.

The statement of Piorry, that a large dose of quinine would produce a distinct immediate lessening of the size of the spleen in cases of intermittent fever, appears not to be correct.

Piorry, Kuchenmeister Mosler and Jerusalemsky have stated that the exposed spleen of an animal can be seen to contract when quinine sulphate is injected into the stomach, veins, or cellular tissue; but Magendie and Bochefontaine have failed in their attempts to produce this asserted contraction. The experiment necessitates such abnormal exposure of the organ that only a very pronounced and very constant diminution could establish the assertion that quinine produces contraction of the spleen, and our present knowledge indicates that the alkaloid has no immediate decided influence on the size of the organ.

*Circulation.*—In ordinary dose, quinine has no effect upon the circulation, but as was first shown by Briquet, if given in very large quantities it lowers the arterial pressure. The fall of blood-pressure appears to be due chiefly to the direct depressant action upon the heart muscle or its contained ganglia, but also in part to the action upon the walls of the blood-vessels.

The lowering of blood-pressure, first noted by Briquet, has been confirmed by various observers, notably by Schlockow, A. Eulenberg, and Cerna. It has been abundantly proved that the alkaloid thrown into the jugular vein, introduced into the coronary artery, or in any way brought in contact with the heart, lessens the force and frequency of the pulsations, and finally produces diastolic arrest; also that this result is not influenced by separation of the mammalian heart from the



nerve-centres, and occurs in the cut-out frog's heart. The evidence is conclusive that both in man and in the lower animals *quinine in sufficient amount is a powerful depressant to the heart-muscle or ganglia*.\*

Schroff found that in the quininized animal neither galvanization of a sensitive nerve nor asphyxia was able to produce vascular contraction and rise of blood-pressure, and Jerusalimsky asserts that in frogs dilatation of the vessels can be seen.† Further, Kobert, experimenting with the excised organs of the warm-blooded animals, and Wild, experimenting with the tortoise, prepared according to the method of Stevens and Donaldson, have found that very weak solutions of quinine sulphate (1 part to 5000) cause enormous dilatation of the vessels, with consequent increased rapidity of passage through them of liquid under pressure. It is probable, therefore, that the fall of the arterial pressure in poisoning by quinine is in part the result of an action upon the vessels.‡

Both Schroff and Jerusalimsky noticed that the fall of arterial pressure produced by quinine is preceded by a rise of the pressure, accompanied by an increase of the cardiac action. This observation has been confirmed by G. Sée and Bochefontaine; but no observer seems to have shown that the rise of pressure is more than a temporary phenomenon. The primary rise of pressure may be the result of a stimulant action upon the vaso-motor centres, as Jerusalimsky found that it was not produced after division of the cord. It is not improbable that it is due to disturbances of respiration.

We have never been able to perceive any depressant action upon the circulation in man after ordinary therapeutic doses (three to five grains) of quinine, and we believe that in tonic doses quinine produces no perceptible sedation of the circulation, but that the largest antiperiodic doses have a distinct influence.§

*Blood.*—In 1867 Binz announced that the addition of quinine to human blood, in the proportion of one part to 4000, arrests the amœboid movements of the white blood-corpuscles. It has also been shown that quinine lessens the diapedesis of the corpuscles through the capillaries of frogs. It is questionable how far this effects bears any relation to the therapeutic value of the drug.¶

The present evidence makes it probable that the toxic dose of quinine has a demonstrable action upon the white blood-corpuscles, but that therapeutic doses have no apparent influence.

Confirmation of Binz's discovery has been furnished by Scharrenbroich, by Kerner, by Geltowsky, and by Jerusalimsky. The minimum effective strength of the solution has been found to vary in different species of animals, and even in different individuals of the same species.

\* Pantellejeff (*Centralbl. f. Med. Wissensch.*, 1880, xvii. 529) states that atropine will cause the heart arrested by quinine to recommence its action.

† M. Chirone believes that by quinine the heart is arrested in active dilatation. The theory is very improbable. See *Rivista Clinica di Bologna*, abstracted in *Journ. de Physiol. Norm. et Patholog.*, 1876, 844.

‡ Heubach, in a series of experiments on the influence of galvanization of a sensitive nerve upon the circulation after the exhibition of quinine, failed to detect any paralyzant action of the drug, although in some of his experiments the reflex activity was paralyzed.

§ When, in Wild's experiments, the action of quinine was maintained for a length of time, the dilatation was finally followed by contraction, which contraction was in all probability the outcome of a post-mortem rigidity.

¶ Some studies have been made upon the action of the drug on the capillaries of the brain, but the evidence is contradictory and insufficient. Consult *Psychological and Medico-Legal Journal*, 1875, 33; also *Archives of Medicine*, i. 33.

¶ Binz states that both conine and camphor act more forcibly upon the white corpuscles out of the body than does quinine, and T. Lauder Brunton and Theo. Cash have found that morphine, veratrine, and codeine check the ozonizing power of the blood, while digitalin, picrotoxin, and caffeine increase it.

Binz has studied the mesentery of curarized frogs, to which quinine had been given, exposed upon the stage of the microscope. He found that no accumulation of white blood-cells in the small vessels, or passages of them out into the tissues, occurred upon irritation; or, if after a time these phenomena commenced, they were at once checked by a small hypodermic injection of the alkaloid. When the inflammatory process had already commenced in a "Cohnheim frog," an injection of quinine would cause the out-wandering of the corpuscles to cease, and would bring about a gradual clearing of the white cells from the choked-up vessels. Binz further took two young cats and, after poisoning one of them with quinine, examined their blood. In the blood of the unpoisoned animal the white cells were far more abundant than in that of the poisoned cat. From these facts Binz deduced the conclusion that quinine acts destructively in the system upon the white blood-corpuscles, in the same way as when they are out of the body. George R. Cutter and H. A. Hare have experimentally confirmed the effect of quinine in preventing the extrusion of white blood-cells from the frog's mesentery, and A. Martin has also found that the action of the drug is apparent in the centre of parenchymatous organs, such as the liver.

Schwalbe \* could detect no difference in the blood of a cat before and after poisoning by quinine; and the experiments of Geltowsky upon frogs and guinea-pigs have yielded similar results: in all his animals after fatal poisoning by the alkaloid the movements of the white corpuscles were very active. In a series of experiments H. A. Hare found that the vessels in the cinchonized frog were much more contracted and had their walls much thicker than in a corresponding frog without quinine. This contraction of the vessels is thought by Hare to be the result of a direct action exerted by the drug upon the muscular coat of the arterioles. It is certain that the alkaloid reduces very markedly the force of the heart. The theory that quinine prevents the out-wandering of the blood-corpuscles by lessening the force which is driving the corpuscles and at the same time increasing the resistance of the capillary walls, seems to us, however, scarcely sufficient; moreover, E. Maurel has found that when the minimum fatal dose of quinine is given to the rabbit the leucocytes take on the rounded form which is characteristic of the early stage of the quinine action in drawn blood.

Upon the red blood-corpuscles quinine exerts a distinct influence in inhibiting their functional activity.

When blood is drawn from the body and allowed to stand, acid is developed in it (see Zunst). Binz believes that this development of acid is due to oxidation, and by an elaborate series of experiments has determined that quinine (also berberine sulphate and sodium picrate in almost as great degree) inhibits these changes very greatly. These experiments are in accord with the previous ones of A. Schulte: the facts may, therefore, be considered proven.

Binz and his pupil, Ransoné, have determined that quinine also inhibits oxidizing power of blood as shown by the turpentine-guaiac test, one part of it added to a thousand of the mixture delaying the change of color for an hour. In these experiments Binz used a large number of different salts of quinine, and found that they acted identically. He also found that in young cats to which he had given a very large but not fatal dose of quinine the freshly drawn blood affected the tincture of guaiac much less than it normally should. According to Maurer one per cent. of a quinine salt added to fresh blood rapidly destroys the red disks.

*Uterus.*—Quinine has been largely used as a uterine stimulant. It seems, however, to be well proven that it is not capable of causing abortion, that is, of originating uterine contractions, and the only evidence of its effect upon this organ is from clinical reports.

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\* Quoted by Kerner (*Pflüger's Archiv*, i. 203).

The answer to the question, Has quinine ecboic qualities? should be made out in three different directions. First, Is there any evidence of quinine producing abortion in healthy women or in females of the lower animals? Second, How strong is the evidence of its producing abortion in women suffering from ague? Third, What is the evidence in regard to the action of quinine during labor?

In regard to the first of these sub-questions, the only affirmative evidence we have met with is in the experiments of Rancillia, who saw abortion in two bitches follow the administration of from six to nine grains of quinine: as the pups in one case were already dead before the administration of the drug, it would seem that this investigation was not on such a scale as to be at all conclusive. Moreover, we have given quinine to two pregnant cats, in one case in sufficient quantity to cause death, without disturbing the products of conception. Furthermore, we have met with no evidence that quinine is capable of inducing abortion in healthy pregnant women. Sayre's case is certainly no proof whatever that quinine will originate labor, as labor had commenced under the influence of the hot and cold douche and other measures employed *before* the quinine was given. Chiara, of Milan, has furnished very strong evidence that quinine is incapable of originating uterine contractions in healthy pregnant women. In his public service, two doses of a gramme (15.34 grains) each were given without effect daily for two successive days to eight women, all in the eighth month of pregnancy. It being necessary to cause abortion, one gramme was given daily to one woman for seven days, and to another for three days, without, in either instance, any effect, so that the labor had to be brought on in the usual manner.

The occurrence of abortion in pregnant women, to whom quinine has been given for the relief of malaria, appears to be due to the disease rather than the drug. Malaria often induces abortion, and Erwin, James C. Harris, and A. Russwurm testify from personal experience that quinine will arrest abortion from such cause. J. A. Ashford, Beauchamp,\* Rooker,\* J. S. May,\* and A. d'Arcourd have given quinine to hundreds of pregnant women, suffering from malaria, in large doses without disturbing the uterus.

*Voluntary Muscles.*—C. G. Sauterson, in a series of experiments upon both cold- and warm-blooded animals, has found that quinine acts directly upon the muscle-fibres, increasing the susceptibility and power of the muscle, but, especially in the cold-blooded animal, causing it to become fatigued more readily than normal.

Quinine causes a very marked decrease in the excretion of nitrogenous principles. That such decrease is due to diminished formation, and not to lessened elimination, seems proved by the fact that in Prior's experiments there was no increase of nitrogenous excretion beyond the normal following the omission of the quinine. It seems, therefore, to be established that quinine has a direct or indirect depressing influence upon the tissue-changes of the human organism.

That the output of uric acid is lessened by quinine has been shown by Ranke, by H. V. Bosse and by G. Kerner. The latter observer found that, when about nine grains of quinine were taken in divided doses during the course of the day, the urea was decreased not quite one-eighth, the uric acid to a little less than one-half, the kreatinine was slightly increased, and the nitrogenous material decreased about one-ninth. When a very large dose (thirty-eight grains) was taken in the morning, the urea and the kreatinine were each decreased about one-fourth, as was also the collective nitrogenous material; the phosphoric acid was lessened about one-fifth, and the uric acid about four-fifths. Zuntz (quoted by G. Strassburg) found that twenty-five grains of quinine reduced his elimination of urea nearly

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\* See *American Practitioner*, 1870.



forty per cent. A. Schulte also found that 1.8 grammes of quinine depressed the elimination by the kidneys thirty-nine per cent; yet in the experiments of Unruh the action of the alkaloid in depressing urea elimination was not constant, and in the trials of H. Oppenheim the excretion of urea was actually increased. Nevertheless, the experiments, upon the dog, of Rabuteau and of Hermann von Boeck bear strong evidence to the fact that quinine does decrease the elimination of urea.

Contrary to what might have been expected, Strassburg, in an elaborate series of experiments, found that quinine had no decided effect upon the elimination of carbonic acid either in healthy or in fevered rabbits. These observations of Strassburg are opposed by those of Bock and Bauer, who found that in cats large doses of the alkaloid cause in the first stage of their action lessened carbonic acid production, but that when the convulsions appear the carbonic acid is increased as the result of the increased muscular activity. R. H. Chittenden found that fatal doses of quinine given to fasting rabbits had no decided effect upon carbonic acid production until just before death, when both the animal temperature and the excretion of carbonic acid fell distinctly. On the other hand, small doses of quinine seemed to cause a gradual falling off in the carbonic acid elimination. Although the evidence is somewhat contradictory, it indicates that any action of quinine upon carbonic acid elimination must be very feeble and uncertain.

**Temperature.**—The drift of our present clinical evidence seems to indicate that quinine exerts in febrile disease a decided antipyretic action, which is especially manifested during those stages of disease in which the natural tendency is towards a lowering of temperature. In exanthematous diseases, etc., after the use of the cold bath twenty grains of the alkaloid are often efficacious in delaying the return of the excessive fever.

Unless given in enormous toxic doses, quinine does not lower bodily temperature in health. It is alleged, however, by G. Kerner and Jürgensen that it will largely prevent the rise of the bodily temperature which normally occurs from exercise, and it is asserted by various clinicians that it does not affect the temperature in fever. C. Liebermeister came to the conclusion that quinine given in doses of from twenty to forty-five grains in one hour is, in typhoid fever, a very active and certain antipyretic, a conclusion also reached by the Committee of the London Clinical Society.

Naunyn and Quincke found that sometimes quinine prevented the development of fever after the division of the spinal cord in animals, but in other cases failed to do so. Binz has achieved similar results: he says that if the conditions of the fever are too favorably constituted the effect of the quinine fails thoroughly.

**Therapeutics.**—At present our estimate of the value of quinine in disease, and our knowledge of its therapeutic use, rest solely upon clinical observation, although recent discoveries have enabled us to frame a very plausible explanation of the method by which it overcomes malarial disease.

On account of its power of arresting or preventing putrefactive fermentation by killing the microscopic entities which produce such changes, Binz has recommended quinine in the so-called *septic diseases*.

The chief evidence which he produces is in some ten experiments made upon dogs and rabbits. In each of these experiments two similar animals were poisoned with putrescent liquids, and to one of the pair quinine was freely administered. In two cases the cinchonized animal recovered, while its fellow perished; in three experiments neither of the animals died; and in the other five trials the cinchonized animal lived from two to twenty-four hours longer than the other. These experiments are certainly too few and indecisive to prove in any degree Binz's view. To us they indicate very strongly that quinine has no such influence over the disease as he believes. If living germs in the blood were really the cause of the septic symptoms, and if quinine killed such germs, its action would be as manifest and as unmistakable as it is in intermittent fever.

The results of Binz's experiments seem to us to agree with the emphatic teachings of clinical experience that quinine has no direct specific influence in *pyemic*, *septic*, or *exanthematous* diseases.

As a simple tonic, quinine is largely used, especially in combination with iron. We are not entirely convinced that it is of much more value in simple debility than is quassia or other simple bitters; but if, as is probable, it be true that quinine lessens to a very great extent the elimination of nitrogen,—*i.e.*, the consumption of tissue,—the general practice is well founded. Hare, as the result of observations made upon himself, believes that quinine has a distinct action in increasing the formation of the red blood-corpuscles. If this be correct, it must have especial tonic value.

Large doses, sixty to seventy grains, of quinine have been used by Briquet and other French physicians in inflammatory rheumatism; under these heroic doses the symptoms of inflammatory rheumatism have often rapidly abated; but the method has found little favor out of France, and is less efficient and more dangerous than other plans of treatment now in vogue. In *inflammatory rheumatism*, after the acute symptoms have abated, when the patient shows evident signs of weakness, especially if there be profuse sweating during sleep, fifteen grains of quinine daily are often of great service.

Conceiving the theory that choreic movements may be due to weakness of the spinal inhibition, H. C. Wood some years ago injected quinine into the veins of choreic dogs, and found that the movements were at once arrested by comparatively small doses of the alkaloidal salts. This led him to make trial of the remedy in the *chorea* of childhood, and as the result of much experience it has been determined that the drug in some cases of this affection is of great value. There are certain cases in which enormous doses are borne without the production of cinchonism: thus, we have given in a month to a child ten years old one thousand grains of the quinine sulphate without causing tinnitus aurium or other disagreeable effect, but with the result of curing a chorea which had resisted all treatment for nearly two years. In our experience in the disease, when there is no tolerance of quinine no benefit is achieved by its administration, but when the quinine is tolerated in large dose its use is commonly most beneficial. Led by the results obtained in chorea, the chief of H. C. Wood's clinic at the University Hospital, Charles S.

Potts, conceived the belief that *incontinence of urine* might in many cases be the result of failure of inhibition, and on trial found that very large doses of quinine often put an end to this most annoying symptom, a result which we can confirm from our own experience. Quinine salicylate is often effective in subacute *muscular* and *neuritic rheumatism*, or in the subsiding stages of *acute rheumatism*.

The chief value of quinine is as an *antiperiodic*. There is at present little doubt that the alkaloid does good in all forms of malarial fever by directly affecting the malarial plasmodium or organism.

Quinine in its relations to *malarial fever* may be considered, first, as a prophylactic; second, as a curative agent.

The value of the daily use of quinine to persons exposed to a malarial atmosphere has now been thoroughly tested in all portions of the world. In North and South America, in Europe, in Africa, and in India the prophylactic powers of quinine have been tried on the largest scale in connection with the military and naval services, and the testimony is unanimous in favor of the drug.

A single citation will serve to illustrate this fact. J. B. Hamilton reports the case of a battery of one hundred and thirty-five men, quartered at Jubbulpore, East Indies, in the same barracks with an infantry regiment. Each of the artillerymen received three grains of quinine every other day: to the infantry none was given. The result was that while three hundred out of the five hundred men of the regiment were sick at one time with malarial disease, at no period was more than four per cent. of the battery affected.

The dose of quinine as a prophylactic may be considered as two grains in the morning and three grains in the evening.

In *intermittent fever*, when there is sufficient time, it may be well to precede the quinine by a mercurial or other purge. If the expected paroxysm be so near that there is not sufficient time for the action of the purgative, the antiperiodic should be administered without previous preparation of the patient. The value of purgatives in obstinate intermittents, as an adjuvant to quinine, is often overlooked, although in some cases the employment of purgatives, and of such diuretics as cream of tartar, seems to be almost essential for the successful use of the antiperiodic.

In *pernicious fever*, or *malignant malarial poisoning*, no time should be lost after the first paroxysm in getting the patient cinchonized, as it may be uncertain whether the attack be of the quotidian or of the tertian type. At least sixty grains of the alkaloidal salt should be administered during the first twenty-four hours; in very severe types of the disease even larger doses than these are necessary, less than seventy-five grains of the drug sometimes being unable to suppress the disease.

In *remittent* or *bilious fever* it may often be advisable to give purgatives and febrifuges before the quinine. As soon as the remission has appeared, the exhibition of quinine should be begun. Local inflammations or even severe cerebral symptoms occurring during



a remittent fever are no contraindications to the use of the specific. When gastritis exists, other channels of entrance than the stomach should be employed, on account of the local irritant action of quinine.

When the symptoms in remittent fever are severe and seemingly continuous, it may be not only proper but necessary for the saving of life to exhibit quinine freely during the period of fever. In large doses the alkaloid is probably antipyretic as well as antiperiodic, and we do not know of any theoretic or clinical objection to its use during the period of fever.

In *malarial intermittent neuralgia*, as in all other forms of abnormal manifestations of malarial disease, quinine is efficient, although it is usually necessary to administer it in large doses (thirty to forty grains at intervals).

In *neuralgia* which, although not dependent upon malaria, assumes the intermittent type, quinine will often temporarily set aside the paroxysmal attacks, and sometimes effect a cure. The same fact may be stated in broad terms as true of *all non-malarial intermittent affections*. In the great majority of such cases, unfortunately, the action of the quinine is only temporary, and any controlling power is soon lost.

Ordinarily the best method of treating a case of intermittent fever is to give the patient a full mercurial purge, and after it has acted, to begin the exhibition of the drug about eight hours before the expected paroxysm, in doses of five grains every two hours until from fifteen to twenty grains are taken; care being exercised to see the quinine is in such form as to secure prompt absorption. In cases of persistent or chronic intermittent fever, quinine is often administered in moderate doses day after day, but we are convinced that it is better to use the remedy in large doses at intervals than to administer it continuously in smaller amounts. In this climate fifteen grains of quinine a day will usually put an end to a mild intermittent, but the paroxysm will be likely to recur, even if six grains of the alkaloid be afterwards given daily for some weeks. We believe it is better to administer from twenty to twenty-five grains in the beginning, sufficient to produce very pronounced cinchonism and to arrest the disease at once. The full physiological effect of the drug should then be maintained for two or three days, and no more quinine given except at certain intervals. The paroxysms have undoubtedly a great tendency to return on the seventh day after their arrest, and every seventh day for some weeks full cinchonism should be produced. If the observation of Councilman, that large doses of quinine entirely destroy the malarial organism, be correct, the practice just spoken of has a foundation in scientific as well as in empiric observation.

The general clinical experience, that it is best to administer quinine so that the last dose will be given about two hours before the development of the paroxysm, is confirmed by the various experiments which have been made upon the relation of quinine to the malarial paroxysm. (See Golgi.) Monaco and Panichi believe it proven by their experiments, that the results obtained are not due to the quinine

acting more powerfully upon the young forms of the parasite liberated by the processes of segmentation just before the febrile outbreak, but are due to the facts that quinine remains in the blood during the fever, and that the old parasites present during the febrile stage are more susceptible to the action of the quinine than are the younger forms, even though the latter be not protected by the red blood-disks.

*Local Use of Quinine.*—The effect of quinine upon the lower organisms has suggested its local use in various disorders *supposed* to depend upon the presence of such entities. Thus, Henke, finding some peculiar motile cells in the sputa of *whooping-cough*, employed inhalations of quinine with asserted good results. Henke was not, however, the first to suggest either this fungoid pathology of whooping-cough or the use of quinine. Binz in 1870 asserted that quinine had a specific action in whooping-cough, provided it was given in large doses in solution, so as to come in contact with the mucous membrane in its passage through the pharynx; and in 1871 Letzerich announced that whooping-cough was due to a fungus in the lung. Dawson has confirmed the value of the method of Binz; but, if the fungoid theory be—as we do not believe—true, the plan of Henke must certainly be the better one. The use in *hay-fever*, as recommended by Helmholtz, of a weak tepid solution (one to three grains to one fluidounce), as nearly neutral as possible, freely applied to the nasal mucous membrane, has not achieved general recognition, and any influence which the alkaloid has in either whooping-cough or hay-fever probably depends on its direct influence upon the mucous membranes. In the later stages of *gonorrhœa* the topical employment of its solution (five to ten grains to one fluidounce) may be serviceable.\*

**Administration.**—Ordinarily quinine is used in the form of the sulphate. The powder should be given in capsules, the pill, and especially the sugar-coated pill, being prone to become hard and uncertain in its solubility and action. If immediate action is required the solution may be used, the solubility of the salt being guaranteed by the addition of one drop of dilute sulphuric acid to every grain of the salt. The quinine hydrochloride is as efficacious as the sulphate, and more soluble.

*Hypodermic Use.*—Owing to its local irritative action, and the insolubility of its ordinary salts, quinine does not lend itself well to hypodermic medication. Great local disturbances, abscesses, ulcers, and even tetanus, have followed the injection of the sulphate under the skin. Many of these manifestations, however, were undoubtedly due to lack of proper asepsis. Further, in severe pernicious malarial affections, promptness of action is of the greatest importance, and many of the German practitioners believe that, hypodermically given, quinine acts much more favorably as an antipyretic than when given by the mouth.

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\* Walerian Sokolow affirms that the local application of quinine to *wounds* has a very remarkable effect upon the granulation tissue, a similar effect being produced by the administration of the drug by the mouth. (For details, see *Inaug. Dissert.*, 1891, abstracted in *Schmidt's Jahrb.*, 1892.)

Quinine Bisulphate is soluble in 8.5 parts of water, and is preferable to the ordinary sulphate. One gramme (15 grains) of *Quinine hydrochloride* may be dissolved in 1 C.c. of boiling water, and does not precipitate until the temperature reaches 100° F. For hypodermic injection it is better to dissolve the quinine salt, 1 gramme in 2 C.c. of water, and give in two injections of 1 C.c. each if ten grains are required. According to Gagglio, confirmed by Aufrecht, urethan increases the solubility of quinine so that the following formula is permanent at ordinary room temperature: Quinine hydrochloride, 0.5 Gm.; urethan, 0.25 Gm.; distilled water, add 5 C.c. Quinine hydrobromide is soluble in ten per cent. of water containing twenty-five per cent. of alcohol, and its solution has been used to a considerable extent hypodermically.

**Contraindications.**—On account of its irritant properties, quinine must be used with caution when there is irritability or inflammation of any part of the gastro-intestinal tract. It is strongly contraindicated by inflammation of the middle ear, and may greatly and permanently increase dulness of hearing. The statement of M. Friedmann that ergotin, and that of W. B. Dewees that chloral greatly lessens the tinnitus aurium produced by quinine and salicylic acid need confirmation. Irritability of the bladder or other portion of the genito-urinary tract contraindicates the use of quinine: hence it is often badly borne by old men. It is even asserted that it will, in some persons, cause hematuria.\*

**Toxicology.**—The first symptoms of cinchonism, as produced by full therapeutic doses (ten grains) in man, are usually ringing in the ears, slight fulness in the head, and perhaps some deafness. With the use of larger doses these symptoms are intensified: the deafness is very marked, disturbed vision may exist, and the flushed face, with a sense of distention in the head, may point towards a cerebral congestion, which is in some cases relieved by spontaneous epistaxis. In decided cinchonism, giddiness and staggering in walking are very common. After toxic doses, severe headache, delirium, stupor, complete deafness and blindness, dilated pupils, embarrassment of respiration, great weakness, convulsions, paralysis, and finally collapse may result, either comatose or delirious. Quinine deafness usually passes off rapidly, but may be permanent.

More or less complete amblyopia may be produced by quinine and end in permanent loss of sight. In most of the numerous

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\* In certain regions of country persons suffering from malarial poisons have intermittent attacks of hematuria, or probably, to speak more correctly, of methemoglobinuria, in which the hematuria has been attributed by many practitioners to the influence of the quinine sulphate. The facts, however, that quinine never produces methemoglobinuria in healthy individuals, that the attacks are accompanied by chill, fever, and sweat, following, according to Carreau, absolutely the course of the paroxysm of intermittent fever, and that, though quinine is used everywhere, the methemoglobinuria occurs only in certain localities, certainly seem to prove that the attacks are really due to a peculiar form of malaria and not to the quinine. The most elaborate account we have met with is that published in Guadeloupe, in 1891, by J. Carreau (*La Méthémoglobinurie Quinique*, 1891; see also *Bull. Soc. de Méd. Pratique de Paris*, 1891; *Arch. de Méd. Navale*, 1896, lxc., 1897, lxxvii.; *Bull. Thérap.*, xcvii.); Pispiris (*Le Progrès Méd.*, 1891, xix.) affirms that in some cases of malarial fever not only the internal administration but also external friction of the quinine sulphate will provoke serious gastro-intestinal hemorrhage. It does not, however, appear probable that the quinine in his cases was the cause of the bleeding.



recorded cases the amount of quinine ingested has been very large, but we have seen in one individual twelve grains of quinine repeatedly produce temporary blindness. The disturbance of vision may come on abruptly or gradually. When fully developed it is usually accompanied by dilatation of the pupils, absence of the light reflex, and imperfect response to accommodative effort. There have also been noted nystagmus, divergent strabismus, anesthesia of the conjunctiva, and increased ocular tension.\*

When the blindness is not complete there is usually pronounced contraction of the field, or, in rare cases, scotomata. The disturbance of vision may subside with the specific action of the drug, but it may persist for days or months, or even permanently. The color-sense is probably first affected; certainly it usually does not recover itself until after the return of central vision. The ophthalmoscopic examination commonly, but not always, has revealed pallor of the optic disks, with excessive lessening in the size of the retinal vessels; indeed, in some cases there has been complete obliteration of the vessels of the optic nerve. Graefe has, however, noted quinine blindness with normal ophthalmoscopic appearances, while Dickinson describes congestion of the retina and chorioid, and Gruening and Mellinger record hyperemia of the disk. The pathogenesis of quinine amaurosis in dogs has been studied by Brunner, De Schweinitz, Burabaschew, De Bono, Holden, and Druault. The visual disturbances are due to a degeneration of the ganglion cells of the retina and the optic nerves, which, with the tracts, finally become completely atrophic. The primary lesion is in the nuclei of the cells, where it may be demonstrated ten hours after the injection of the drug. The breaking down of the least resisting elements of the inner retinal layers—the ganglion cells and nerve-fibres—is commonly believed to be caused partly by a lessened blood-supply due to spasm of the retinal vessels and partly by a direct action of the drug on the protoplasm of the cells. An ascending atrophy of the optic nerve follows. The spasm of the retinal vessels has been attributed to an action of the drug on the vaso-motor centres, which is unlikely, and to its influence on the vessel walls or on the perivascular vaso-motor plexus. De Bono's theory, that paralysis of the neuro-epithelium of the retina causes the amaurosis, has not been confirmed.

Owing to personal peculiarities or idiosyncrasies, quinine sometimes causes manifestations entirely unlike those ordinarily seen. Thus, in a case reported by A. Erlenmeyer, the symptoms simulated those of strychnine-poisoning.† In some persons a few grains of quinine produce various forms of dermatitis, the most common of which is a scarlatinoid erythema, although urticaria and purpura have been reported. (For study of quinine skin eruptions see H. C. Wood, Jr.)

The importance of these idiosyncrasies was shown in a case in our own practice, in which two grains given by the mouth produced a furious general urticaria, with great subdermal swelling and cardiac depression of the most alarming character; Micciché reports the death of an adult caused by the hypodermic injection of seven and seven-tenths grains (one-half gramme), the symptoms being great pale-

\* For discussion of the subject, with *resumé* of the literature, see *Toxic Amblyopias*, George E. de Schweinitz, 1896, and Norris and Oliver's *Diseases of the Eye*, 1900, iv. 832; for case of blindness lasting twenty-one days, see *Brit. Med. Journ.*, 1886, i. 823.

According to Rogers (*Journ. Amer. Med. Assoc.*, 1889), one or two hours after the ingestion of twenty grains of cinchonine sulphate there can usually be observed paresis of accommodation, which may increase until it becomes almost complete. It seems hardly possible that this phenomenon, if an habitual one, could have been overlooked by other observers.

† For cases, see *Brit. Med. Journ.*, 1869, ii.; *Berlin. Klin. Woch.*, 1877, 294; *Phila. Med. Times*, x. 166; *N. Y. Med. Record*, xxi. 627.

ness of the surface, small, frequent pulse, high fever, severe nervous depression, increasing stupor with delirium, great dyspnoea, jaundice, hematuria, and anuria. Death occurred on the seventh day. Both during life and at the autopsy the evidences of great destruction of red blood-corpuscles were apparent. Chevallier describes a peculiar affection of the skin, etc., as occurring among workers in the bark.

Fatal instances of poisoning by quinine are rare in literature, but Husemann has made a collection of cases in which death has been attributed to the alkaloid,—not always, in our opinion, with correctness. The minimum fatal dose is not known, but must be very large.

Clapton details a case in which a soldier took at one dose an ounce of the sulphate, stirred up in some water, without the induction of any more serious symptom than a mild stupor; a similar case is mentioned by Lente, on the authority of Woodhull; and a third is recorded by Taussig. R. G. Wharton records a case in which during thirty-six hours a half-ounce was taken without vomiting and without ill effect. We cannot help suspecting that in all of these cases much of the drug passed through the intestines without absorption. In the famous case of Bazire, five ounces taken in the course of ten days caused death.

**CINCHONINE SULPHATE.**—The pure alkaloid cinchonine crystallizes in prisms and needles. The official cinchonine *sulphate* is in short oblique prisms of a very bitter taste, soluble, at 77° F., in fifty-eight parts of water, more freely in boiling water, readily soluble in alcohol.

**Physiological Action.**—Conzen (quoted by Husemann) has found that the action of cinchonine on infusoria and on fermentation is similar to but weaker than that of quinine, and that on the movements of the white blood-corpuscles its influence seems transient. It is stated that it is eliminated unchanged and rapidly, the great bulk of it being thrown off in the first twenty-four hours. According to the experiments of Laborde and Bochefontaine, toxic doses cause in the lower animals more violent epileptiform convulsions than do the corresponding doses of quinine. In Bochefontaine's experiments the relative strength of cinchonine to quinine was about 10 to 16, in Bernatzik's (on dogs only) as 4 to 5. De Schweinitz has found that cinchonine produces amaurosis in the dog, as does quinine.

**Therapeutics.**—As an antiperiodic, cinchonine exerts a similar influence to quinine, but is probably about one-third weaker than that alkaloid, and must be used in correspondingly larger doses. J. B. Hamilton affirms, as the result of experiment, that cinchonine as a prophylactic against *malaria* is even superior to quinine. As a tonic we have never been able to perceive that cinchonine acts differently from quinine.

**CINCHONIDINE SULPHATE** occurs in white, silky, lustrous needles or prisms, odorless, of a very bitter taste, soluble in sixty-three parts of water, freely soluble in acidulated solutions. It polarizes to the left, and is not fluorescent. According to Sée and Bochefontaine, cinchonidine produces in the lower animals symptoms similar to those caused by quinine, except that the convulsions are less severe.

A boy aged five years took one hundred and twenty-eight grains in solution during six hours without vomiting. There were then convulsions followed by great collapse, fall of temperature, pulselessness (with seventy-four cardiac beats per minute), dilated pupils, muscular relaxation, and, finally, death; consciousness was preserved to the end.\*

Cinchonidine acts similarly to quinine, but is less powerful, doses one-third greater being required. The assertions made by various clinicians, that it produces less disagreeable symptoms than does quinine, have not been confirmed. De Segrays has found the hydrobromide given hypodermically in doses of four to six grains (0.26-0.4 Gm.) very efficacious.

**WARBURG'S TINCTURE.**—This is a dark brown liquid, prepared in accordance with a very complicated formula,† which has obtained an extraordinary reputation in India and other tropical countries in the treatment of severe *remittent* and malignant *malarial fevers*. The testimony is so strong as to its remarkable and almost certain efficiency that it cannot be questioned, and entitles the tincture to rank above all other remedies. The method of administration is as follows. The bowels having been freely opened, a half-ounce of the tincture is given undiluted, all drink being withheld, and at the end of three hours a second half-ounce is in similar manner exhibited. Soon after the last dose a profuse aromatic perspiration sets in, and convalescence is usually secured. The remedy is also commended in one-drachm dose in acute *nervous exhaustion* and *collapse* without organic disease.

**QUININE ESTERS.**—A number of the esters of quinine have been examined pharmacologically, and some of them have found their way into practical use. Among these compounds acetylquinine has been condemned on account of its taste; benzoylquinine and phosphorylquinine are stated by M. Overlach to be practically inert. The esters which have been put upon the market as of value are as follows:

**ARISTOCHIN.**—*Neutral carbonic quinic ester.*—This tasteless, pinkish-white, amorphous powder, soluble in alcohol, ether, chloroform, or glycerin, insoluble in water, is said to contain ninety-six per cent. of quinine. According to Stursberg, after its ingestion, quinine appears in a short time freely in the urine. It probably is effective as an antiperiodic, but has been chiefly commended in *whooping-cough* of children, given in doses of from one to four grains three times a day.

**EUQUININE.**—The *ethylcarbonic ester of quinine* has been highly commended as a substitute for quinine, and as having the advantage of being practically tasteless and of producing a less severe tinnitus aurium. The tinnitus aurium is, however, almost certainly a test of the amount of active quinine in the circulation; that euquinine is absorbed very slowly and eliminated very slowly is indicated by the studies of F. K. Kleine, who was unable to obtain from the urine more than seventeen per cent. of the quinine contained in the ingested euquinine. It does not, therefore, appear probable that euquinine is as efficient as quinine, but it has been commended highly in all forms of *malarial disease*, also in *whooping-cough*, *chorea*, *anemia*, *general debility*, and, indeed, in all affections for which quinine is generally employed. According to Luigi de Carlo, combined with benzonaphthol it is

\* See *N. Y. Med. Journ.*, 1884, xxxix.

† For complete formula, see *United States Dispensatory*, 19th ed.; the simplified preparation of the National Formulary (Tinctura Antiperiodica) is the one commonly employed to-day.



especially effective in those forms of malaria accompanied by intestinal affection. From fifteen to thirty grains may be given in the course of the twenty-four hours.

**SALOQUININE.**—This *quinic ester of salicylic acid* occurs in colorless crystals, insoluble in water, but soluble in alcohol and ether. It contains fifty per cent. of quinine. Overlach alleges that it does not cause cinchonism; it is, therefore, probably as an antiperiodic very feeble, a conclusion which is confirmed by the fact that F. K. Kleine was only able to recover during the twenty-four hours from two to seven per cent. of the quinine contained in an ingested dose of saloquinine. Nevertheless, saloquinine has been most highly commended as an antiperiodic, as an antipyretic in *fevers*, and as an analgesic and antirheumatic in *neuralgias*, *neuritis*, and similar conditions. It has usually been given in the single dose of thirty grains. In *sciatica* and various *neuralgias* the dose may be repeated within the twenty-four hours. The absorption of the drug appears to be very slow, so that in typhoid fever thirty grains of it, administered directly after the cold bath, begins to exert its influence about the time the effect of the bath is passing off.

### METHYLTHIONINE HYDROCHLORIDE. METHYLENE-BLUE.

*Medicinal methylene-blue* (*Methylthionina Hydrochloridum*) is to be carefully distinguished from the dye-stuff, which is a mixture of the chlorides of zinc and tetramethylthionine, and contains various impurities of which the most important is arsenic. When intended for internal use the drug must be free from arsenic and zinc. Parenski and Blatteis attribute the various unpleasant symptoms—nausea, vomiting, strangury, and the like—which have been reported, to the confusion of the medicinal with the dye methylene-blue.

*Absorption and Elimination.*—Methylene-blue is readily absorbed from both the subcutaneous tissues and mucous membranes of the alimentary tract, appearing in the urine, according to Achard and Castaigne, within half an hour after its hypodermic injection. Although the bulk of the drug ingested probably escapes with the urine, the bluish saliva and feces observed by Ehrlich and Leppmann would indicate that other glands share in its elimination.

In a number of morbid conditions the urine does not become discolored after the administration of methylene-blue.

Achard and Castaigne, believing that this was due to failure of elimination, suggested the remedy as a test for the permeability of the kidney and reported a number of cases of nephritis tending to support their position. Subsequently, however, Voisin and Hauser showed that if this colorless urine be warmed, or if acetic acid be added to it, the blue color will appear. Achard and Castaigne, in reply to this, expressed the opinion that methylene-blue was eliminated in part unchanged, and in part as a colorless chromogenic substance, and that the diseased kidney permitted the passage of the latter but not of the methylene-blue itself; they give, however, no indication of the chemical nature of this chromogen.

*General Action.*—Very little is known concerning the physiological action of methylthionine. According to Combe male and Francois doses of 0.4 gramme per kilo produced in the dog vomiting, purging, and diuresis. These observers found that in the guinea-pig 0.3 gramme per kilo caused muscular weakness, greatly accelerated respiration, and death. After death there was widespread staining of the tissues,

especially marked in the nervous system. The blood was chocolate-colored and contained methemoglobin. Gautrelet and Gravillat state that methylene-blue produces a marked diminution in the urinary excretion of nitrogen.

**Therapeutics.**—In 1890 Ehrlich and Leppmann called attention to the analgesic action of methylene-blue, reporting several cases of *neuralgic* and *rheumatic pains* relieved by it. Combemale and Francois found that while in simple *neuralgia* it was frequently of service,

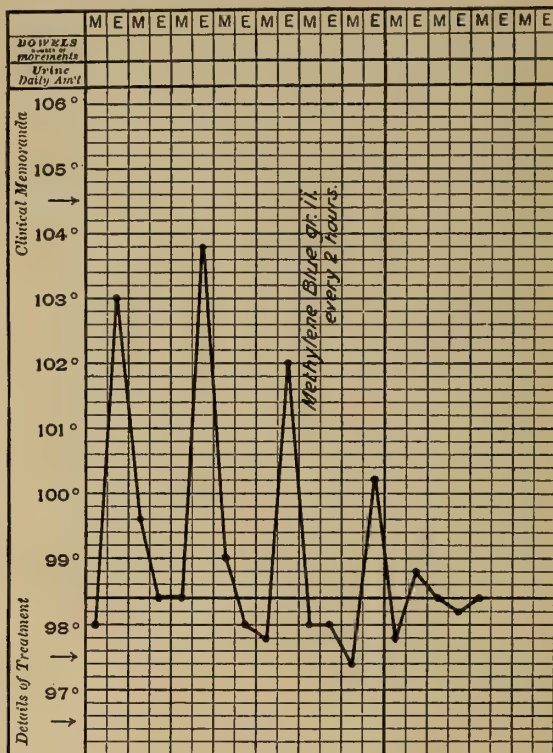


FIG. 15—THE EFFECT OF METHYLENE BLUE IN A CASE OF TERTIAN MALARIA.

The continuous administration of two grains every three hours led to a rapid but not abrupt cessation of the paroxysms with eventual complete cure.

in *neuritis* and central nerve-pains it was of little value. Although numerous other authors have confirmed the statement that methylene-blue possesses some analgesic action, the drug seems to be uncertain in its effect, and has no advantage over the newer aniline derivatives.\*

As an antiperiodic, methylthionine deserves a position of high rank, rivalling quinine in the treatment of *malaria*. In four hundred and twenty-five cases collected by H. C. Wood, Jr., in which it was the

\* The theory of Ehrlich that methylene-blue acts as analgesic by staining the axis cylinders has been shown by Combemale and Francois to be untrue, for while it is possible to stain living tissue with the drug, doses far in excess of those used are necessary.

sole drug employed, there were 85 per cent. (362) of recoveries. Both Rosin and Iwanoff have shown that it exerts a direct, destructive action on the plasmodium malariae. The latter observer states that this effect is most marked in the adult forms of the protozoön, in this contrasting strongly with quinine (correct (?); see p. 431, small print), and that the crescent type, notoriously resistant to cinchona, is easily destroyed by methylene-blue. Since it exerts no irritant influence on renal structure methylene-blue has been recommended especially in the so-called *black-water fever*. Whenever in a malarial disease quinine is contraindicated it is the most serviceable substitute we possess.

Jacobi recommends methylthionine in the treatment of inoperable *cancer*. Slack has also used the treatment with good results.

Austin Flint (1895), impressed with the results obtained from the use of methylthionine in cases of *chyluria*, suggested its use in *gonorrhœa*, concluding from its action on the genito-urinary tract that it would prove to be a valuable remedy in that affection. The results obtained at the hands of many clinical observers do not, however, confirm this opinion, experience showing that where the remedy is employed alone, and not in combination with well recognized anti-bleorrhagic drugs, it has no effect whatever in lessening the urethral discharge. The property which the drug possesses of coloring the urine is, moreover, a distinct disadvantage, as it prevents the physician from drawing proper conclusions regarding the natural appearance of the urine. Methylthionine may be set down as a mild genito-urinary antiseptic of some value in chronic *cystitis* and *pyelitis*.\*

**Administration.**—In the treatment of malarial diseases with methylthionine it is necessary to continue the use of the drug for some time after the cessation of symptoms on account of the liability of relapse. From two to three grains (0.1–0.2 Gm.) may be given every three hours for ten days, and after this, three grains three times a day for a fortnight longer. In gonorrhœa the usual dose is two or three grains (0.1–0.2 Gm.) three times a day. The remedy may be conveniently given in pill form, but preferably enclosed in gelatin capsule to avoid the staining of the fingers and lips. The patient should always be warned of the probable discoloration of the urine.

### EUCALYPTUS.

Of the Australian genus *Eucalyptus*,† which comprises about one hundred and thirty-five species of evergreen trees, the U. S. Pharmacopœia recognizes only *E. Globulus*, whose leaves are official, but

\* This paragraph was written by Prof. H. M. Christian.

† Attention was first called by Labillardiere in 1792 to the value of the *Eucalyptus Globulus* but it was not until 1860 that M. Ramel commenced the culture of the tree in Paris and induced the Prefect of the Seine to order its cultivation on a large scale. Since that time it has been largely introduced into Europe, Algeria, South Africa, and California, and in some of these countries planted forests are now growing and spreading. The tree is remarkable for combining extreme hardness of wood with a rapidity of growth asserted to be about five times that of our ordinary trees; it is also affirmed that shingles made of it are fire-proof. Its capability for absorbing and evaporating water is extraordinary, and to it has been attributed the freedom of Australia from malarial climatic



allows the oil of eucalyptus to be distilled from fresh leaves of various species of the genus. From the various species of *Eucalyptus* are prepared in Australia a number of volatile oils, and also the *Eucalyptus Gum* of the British Pharmacopœia. The so-called *red gum*, which occurs in commerce in kino-like grains or masses, contains nearly five per cent. of tannic acid, and is much used in making astringent lozenges.

Most of the eucalyptus oils are composed very largely of eucalyptol or of phellandrene. The oils containing *phellandrene* were thrown out by the revisers of the U. S. Pharmacopœia, evidently under the impression that the active physiological portion of the oil is eucalyptol. Concerning the physiological action of phellandrene, however, we have no knowledge.

The oil of *Eucalyptus* (U. S. Pharmacopœia) is a colorless or faintly yellow liquid, of a characteristic, somewhat camphoraceous odor and a spicy, disagreeable taste. It is generally considered to owe its activity to encalyptol (cineol) of which it contains about fifty per cent. It is to be noted that the oil of cajuput contains the same active principle in and about the same proportion and is probably therefore therapeutically equivalent to the oil of eucalyptus.

The *Oil of Cajuput* is obtained from the leaves of *Melaleuca Leucadendron*, a tree growing in the Molucca Islands. This volatile oil is of a green color, a peculiar fragrant odor, and a burning, camphoraceous taste.

#### Official Preparations:

Fluidextractum Eucalypti.....	30 minims (2 C.c.).
Oleum Eucalypti.....	10 to 15 minims (0.6–1.0 C.c.).
Eucalyptol (Cineol).....	5 to 10 minims (0.3–0.6 C.c.).
Oleum Cajuputi.....	5 to 10 minims (0.3–0.6 C.c.).

**Physiological Action.**—*Local Action.*—*Absorption and Elimination.*—The oil of eucalyptus is decidedly irritant, large doses causing burning in the mouth and fauces, with increased secretion of saliva, followed very soon by a feeling of warmth in the stomach. It is absorbed from the alimentary canal, and is probably eliminated by the lungs, skin, and kidneys. In the experiments of Binz, the day after the ingestion of seventy-five drops the breath smelt of the drug and the perspiration of amyl alcohol; the urine began to have the odor of the oil an hour and a half after its ingestion, and continued

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influences. Indeed, it is stated that a tree will evaporate ten times its weight of water in twenty-four hours, and numerous examples are given in which swamps in Europe and Algeria have been rapidly converted by it into dry ground. It is believed to destroy malaria not only by draining the soil, but also by yielding balsamic exudations to the air; however this may be, there is at present very strong evidence as to its power of rendering infected districts healthy. As the consideration of this subject belongs to hygiene rather than to therapeutics, the reader is referred for detailed information to the following memoirs: *Regulus Carlotti (L'Eucalyptus, son Rang parmi les Agents de la Matière Médicale, Ajaccio, 1872)*, *M. Gimbert (L'Eucalyptus Globulus, son Importance en Agriculture, en Hygiène, et en Médecine, Paris, 1870)*, *Waterer (Bulletin de la Société d'Acclimatation, 1872; London Medical Record, Dec. 1873; London Lancet, 1877, ii.)*.

Under the name of *Eucalypsinthe*, a liqueur distilled from the leaves of the eucalyptus has appeared in European commerce.

It has been affirmed that the leaves of *Eucalyptus* contain also an alkaloid; but *Rabutaue (Bull. Therap., lxxxiii, 549)* has demonstrated that this is an error.

to have it for thirty-six hours. Gimbert states that the odor imparted to the urine resembles that of violets, and is very similar to that caused by turpentine. Binz affirms that upon the lower infusoria the oil acts even more powerfully than does quinine, and its general antiseptic properties are decided (Gimbert).

*General Effect.*—The constitutional effect of the same dose of the oil appears to vary considerably in different individuals; but the following summary comprises the facts as nearly as may be. After the ingestion of from ten to twenty minims, a period of mental and physical activity is often apparent, followed by a feeling of calm and serenity. After large doses irritation of the digestive organs sometimes shows itself by loose stools or even by vomiting. In exceptional cases even the moderate dose may produce violent cardiac palpitation and intense headache and fever, all these symptoms probably being due to gastric irritation. Large amounts of the oil cause marked depression, with slowing and afterwards quickness and weakness of the pulse, general asthenia, sub-normal temperature, blunting of sensation, and finally profound loss of muscular power with stupor, deepening into unconsciousness, and accompanied by loss of the reflexes, and contracted reactionless pupil.

In anomalous cases the symptoms produced by the oil of eucalyptus differ from the typical character. Thus, in an old man who took eighty drops, the power of motion almost disappeared; the man also affirmed that he lost for the time being all sense of the presence of his limbs, so that he was unconscious of possessing them when he shut his eyes, although his intellect was perfectly clear throughout. In a case reported by Alfred Neale, a little over half an ounce of the oil of eucalyptus is said to have produced death in fifteen hours in a healthy boy: the only recorded symptoms were violent dyspnoea with collapse.\*

Upon the lower mammalia the oil of eucalyptus appears to act precisely as it does on man. According to the experiments of Gimbert, the hypodermic injection of the oil is immediately followed by a period of excitement, seemingly in great measure due to the intense local irritation; after about half an hour, if the dose has been sufficiently large, the animal begins to stumble and totter in walking, the breathing grows more and more slow and irregular, the limbs give way, the ears droop, the muscular weakness becomes profound, and death, preceded often by partial convulsions, occurs through failure of respiration.

Death appears to be produced by the fatal dose through asphyxia. According to the experiments of Gimbert (confirmed by Binz), the motor nerves and the muscles are not affected, so that the failure of motion and reflex activity is probably due to a depression of the motor side of the spinal cord and of the medulla. According to Hermann Schläger, the hypodermic injection of the oil produces a temporary rise of temperature, probably as the result of the local irritation, but after toxic doses the temperature falls decidedly. Schläger also states that the large dose of the oil causes a marked lessening of the arterial pressure, whose coming on is not affected by previous section of the vagi, by atropinization of the heart or by

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\* As a quart of very bloody serum was found in the pleura cavity, and as the boy was not seen professionally until he was *in articulo mortis*, doubt attaches to this case.

section of the cord. It would appear, therefore, that the oil of eucalyptus directly depresses the heart or the peripheral arteries. As in Schläger's experiments the force of the isolated frog's heart was distinctly depressed by the drug, the latter must be a direct cardiac depressant. Mosler affirms that in dogs whose spleens were exposed, injections of tincture of the leaves of eucalyptus produced a decided contraction of the viscus. According to Gimbert, the excretion of urea is enormously increased by the drug.

**Therapeutics.**—The oil of eucalyptus has some power as an antiperiodic, but is much inferior to the cinchona alkaloids and to methylene-blue, and should be used only in cases in which for sufficient reasons these remedies cannot be employed, or as an adjuvant to them.

Joseph Keller used it in four hundred and thirty-two cases, of which two hundred and ninety-three had suffered from previous attacks. Of the tertians 75.57 per cent., of the quartans 70 per cent., and of the quotidians 67.89 per cent. yielded to the remedy. He recommends it as especially valuable in obstinate cases in which quinine has been taken again and again. Lorinser, Haller, Bohn, Carlotti, Cortan, Gimbert, Gubler, Tristany, of Spain, J. H. Musser, and others, bear testimony to the power of Eucalyptus in *malarial diseases*; while Brudell, Seitz, and Papillon affirm it to be of little or no value.

Oil of eucalyptus is one of the best stimulating expectorants that we possess: in both *acute* and *chronic bronchitis* it may be exhibited when there is free secretion. Children bear it very well. According to A. F. Galbraith Faulds, it is valuable in some forms of *glycosuria*. It is also largely used locally as a stimulant antiseptic in various chronic inflammatory conditions of the mucous membranes of the upper respiratory tract.

The oil of cajuput has been used chiefly as an external parasiticide in various skin diseases, also as a local stimulant application in *psoriasis*, *acne*, *rosacea* and *pityriasis*. It is not very irritating to the skin, but is exceedingly destructive to low forms of life, and consequently has been used as a *parasiticide* externally, and even internally against the *Ascarides*. In *intestinal pain* and *spasm* and in *serous diarrhæa* it is efficient, especially in combination with chloroform, camphor, and opium. As a counter-irritant, it has been used in *rheumatism*; as a stimulant to the skin, in *psoriasis*, *acne rosacea*, and *pityriasis*.

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## FAMILY V.—ANTIPYRETICS.

UNDER the term Antipyretics are to be considered certain remedies which are used in practical medicine for the purpose of reducing bodily temperature in fever. Most of these remedies conjoin to their antipyretic properties the capability of relieving pain which is not due to inflammatory or other distinctly local diseases or traumatism.

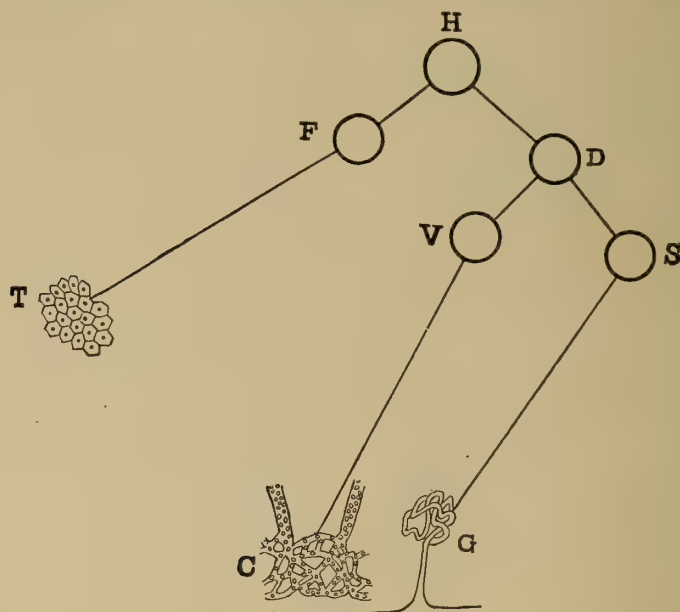


FIG. 16—TO SHOW HOW DRUGS MAY AFFECT BODY TEMPERATURE.

H—Heat-regulating center. F—Center for heat formation. D—Center for heat dissipation. V—Vaso-motor center. S—Center for sweat glands. C—Capillary blood vessels in the skin. G—Sweat gland. T—Tissue cells. Drugs may lower body temperature by diminishing chemical activity in T; or by increasing heat dissipation through dilatation of the skin capillaries or greater secretion of sweat.

Some of them are actively antirheumatic. The different members of the class vary greatly in the activity of what may be termed their secondary properties, some of them being used in reality almost entirely as antirheumatics or analgesics, their antipyretic powers being inferior for practical purposes to those of other members of the group.

The method in which antipyretics reduce fever temperature has not been thoroughly worked out, but it is probable that they exert their influence by an action upon the thermogenetic or thermo-inhibitory centres. On the other hand, it is possible that they have

such immediate influence on the chemical processes in the various tissues of the body as to directly affect the production of heat.

The question as to whether it is better in fever to reduce the excessive temperature by the administration of an antipyretic, or by the use of the cold bath, is one to which at present a positive answer cannot be given. So far as our present knowledge goes the antipyretics produce greater disturbances in the general functions of the body than is caused by what we may call the mechanical abstraction of heat. Further, the fever process itself is a disturbed condition of the nutrition, which is by no means thoroughly comprehended. In the administration of an antipyretic we are attempting to modify for the better a morbid process of whose real nature we are ignorant by the use of a powerful drug of whose action we have not definite knowledge. The use of the antipyretics is at present empiric, and in our lack of knowledge the cold bath would seem to be a safer remedy than the drug. The greater convenience of antipyretics, however, exerts a constant pressure for their use by the physician, and little by little confidence in them seems to be growing. Our own belief is that in minor cases of fever the antipyretic is often superior to the cold bath because of its greater ease of application, but that in the severe cases of fever, especially when there is a tendency to persistent adynamia, the best results are to be achieved by relegating antipyretics to the class of adjuvants, employing them in moderate dose simply for the purpose of assisting the cold bath, and of prolonging its influence.

### SALICYLIC ACID.

Salicylic acid occurs in long acicular crystals or in the form of a white, dull powder, almost odorless but with a sweetish unpleasant taste, accompanied by a transient sense of numbness. It is soluble at 25° C., in about three hundred and eight parts of water and in two parts of alcohol.

Owing to the irritant action on the mucous membrane salicylic acid is very rarely used as an internal remedy. A number of its salts, however, are official. Of these the sodium, ammonium, strontium and lithium salicylates all occur as white powders with the characteristic unpleasant taste of salicylic acid, freely soluble in water and fairly soluble in alcohol. Besides these salts various esters of salicylic acid are also used, of which two are official, methyl and phenyl salicylic esters.

*Methyl salicylate* is an almost colorless but slightly yellow liquid, volatile, with a very penetrating characteristic odor like that of wintergreen. It occurs naturally in a large number of plants but is especially abundant in the wintergreen and sweet birch. The volatile oils of these two last plants contain in the neighborhood of ninety per cent. of methyl salicylate to which substance they owe both their physical and their therapeutic properties.



Oil of gaultheria, Oil of Sweet Birch, and the Methyl Salicylate prepared synthetically are so similar in composition that they *probably* have the same action upon the human economy, but this is not *certain*, and the apothecary should always put up the exact drug prescribed.

The question whether the natural salicylic acid of the oil of gaultheria has any different physiological action from the artificially prepared but chemically identical acid has been elaborately investigated by B. J. Stokvis, who reaches the conclusion that there is a marked quantitative difference, the natural acid being distinctly less poisonous than the artificial,—a circumstance which he thinks is due to the superior osmotic properties of the natural acid, causing it to be more rapidly eliminated.

*Salicin* is a glucoside obtained from several species of willow and poplar. It occurs as colorless crystals without odor and having a very bitter taste, soluble in twenty-one parts of water. Its therapeutic virtues depend chiefly upon the fact that it is decomposed with the formation of a sugar-like body and salicylic acid.

It is readily absorbed, and is eliminated as salicin, saligenin, and salicylic acid (Husemann). According to Scarpetti, it inhibits the functional activity of the red and white blood-corpuscles, but less powerfully than does quinine. It was originally introduced in the treatment of specific and acute *rheumatism* by MacLagan, but its therapeutic activity apparently depends upon the salicylic acid which is produced out of it in the system; and as its conversion is slow and imperfect, as a remedy it is of very inferior value. At present it is rarely used.

#### Official Preparations:

Acidum Salicylicum.....	5 to 15 grains (0.3–1.0 Gm.).
Ammonii Salicylas.....	.5 to 30 grains (0.3–2.0 Gm.).
Lithii Salicylas.....	.5 to 30 grains (0.3–2.0 Gm.).
Sodii Salicylas.....	.5 to 30 grains (0.3–2.0 Gm.).
Strontii Salicylas.....	.5 to 30 grains (0.3–2.0 Gm.).
Phenylis Salicylas †.....	.5 to 15 grains (0.3–1.0 Gm.).
Methylis Salicylas.....	.5 to 20 minims (0.3–1.2 C.c.).
Oleum Betulæ.....	.5 to 20 minims (0.3–1.2 C.c.).
Oleum Gaultheriæ.....	.5 to 20 minims (0.3–1.2 C.c.).
Salicinum.....	15 to 30 grains (1–2 Gm.).

**Physiological Action.**—*Local Action.*—*Absorption and Elimination.*—Pure salicylic acid is so actively irritant to mucous membranes that its less irritant compounds are universally preferred in practical medicine. It is absorbed rapidly through mucous membranes, and also to a less extent through the skin when applied in alcoholic solution (Drasche), or in the form of a soluble compound. It circulates as a sodium or other salicylate. Many of its insoluble compounds, such as strontium salicylate, bismuth salicylate, etc., undergo slow decomposition in the alimentary canal, yielding their salicylic acid to the alkaline intestinal juices, and subsequent absorption.

Salkowski pointed out that salicylic acid in the blood probably exists in the form of the sodium salt. Binz supposes that the acid is liberated in the blood by the carbonic acid formed in the tissues. Feser and Friedeberger found that unless

† Phenyl salicylate is considered in connection with phenol (see page 673.)

enormous doses of the drug were injected into the blood so as to produce immediate violent convulsions and death, no free salicylic acid was demonstrable. In Köhler's experiments, when salicylic acid was dissolved in normal blood no acid was yielded to ether; but when the blood of asphyxia—i.e., blood supersaturated with carbonic acid—was employed, a very notable amount of the acid was extracted by the ether. These experiments warrant the conclusion that when the blood is in the normal condition the alkaline salicylates are not decomposed by the carbonic acid in it.

Feser and Friedeberg have advanced the theory that the salicylic acid circulates in the form of an albuminate. This has received some support from the experiments of Farsky, which seem to show that the acid is capable of forming such a compound.\* On the other hand, the theory is contradicted by the results of Fleischer, who digested albuminous solutions with the acid, and after coagulation by heat found all the acid in the filtrate, and who also treated the blood of poisoned animals in a similar way, and found the salicylic acid only in the serum, the coagulum being free.

Salicylic acid, although it probably enters into every liquid of the organism, escapes from the body chiefly through the kidneys, its elimination beginning almost immediately after its ingestion. It appears to be excreted partly as salicylic acid and as a salicylate, chiefly as salicyluric acid, and partly as, at present, unknown educts.

Ugolino Mosso recovered from the urine, both in man and animals, practically all of the salicylic acid which had been ingested, either in the form of salicylic or salicyluric acid. Stockmann found that from one-half to one-twentieth of the ingested salicylic acid was eliminated unchanged, the greater portion being converted into salicyluric acid. Fürbringer and Drasche failed to detect it in the feces the saliva, the bronchial secretion, or the sweat, but Mussy found it in the saliva as did also Balz, and Oulmont detected it in the serosity of a blister. It appears in the urine very soon after its ingestion, but its elimination proceeds slowly. Thus, in a case of exstrophy of the bladder it was detected in the urine dripping from the ureter eight and a half minutes after its ingestion (Balz), and it has been found in the urine eight days after the exhibition of the last dose (Byanow). The latter observer also found it in the urine of a normal man as a salicylate twenty-five minutes after its swallowing. A. E. Stuart, after so small a dose as nine grains of the acid, saw free, distinct crystals of salicyluric acid in the urine. It is possible that such of the salicylic acid as escapes unchanged from the kidney may, as first excreted, be in the form of a salicylate, but be set free by the phosphoric acid of the urine; at least such would be indicated by the fact that in Balz's case of exstrophy sodium salicylate appeared in the urine twelve minutes before the free acid. The green color of the urine characteristic of the free use of salicylic acid appears to be due to an increase in the formation of indican (S. Wolfberg, M. Robin), or else to pyrocatechin (Sée), and it is not improbable that the pyrocatechin is formed out of the salicylic acid.

*Nervous System.*—So far as we know, the single, even large, therapeutic dose of salicylic acid has no distinct action upon the nervous system, unless it be upon the peripheral ends of the auditory and perhaps other nerves of special sense, the tinnitus aurium caused by it indicating that upon these organs it acts as does quinine. The symptoms of salicylic-acid-poisoning indicate that the drug does act, when in overwhelming dose, upon the cerebral cortex; how far other portions of the nervous system are affected is at present uncertain.

\* He digested various albuminous substances with salicylic acid, washed them with ether until it would take no more acid, dried, washed with water, and found on analysis salicylic acid largely present in the residue.

It is probable that the feeling of depression often produced by the free continuous use of the salicylates is largely the outcome of an influence upon the cerebral cortex.

According to Sée, neither the reflexes nor the general sensibility, nor the conducting power of the nerve-trunks are sensibly impaired in the lower animals poisoned by a salicylate, but Laborde states that a drachm of the salicylate will produce in a dog profound cutaneous anesthesia; and Bochefontaine affirms that in the frog the drug depresses the spinal cord, it may be to the point of paralysis.

*Respiration.*—The respiratory phenomena produced by salicylates in the lower animals are said to be quickening, followed by slowing, of the respiration, with gradual failure until death from asphyxia results. The slowing and final paralysis are probably due to a direct action upon the respiratory centre. The primary quickening has been ascribed with plausibility to irritation of the pulmonary vagi, though it is probable that there is primary stimulation of the respiratory centre.

When, in Köhler's experiments, the pneumogastrics were divided during the period of retardation, the frequency of the respiration was still further lessened. Danewsky practised section of the vagi before exhibiting the drug and during the first stage of accelerated breathing. In the first instance he found that the breathing was only slightly accelerated by the drug; in the second, that the quickened respiration fell to the same slowness that is seen in the unpoisoned animal with cut pneumogastrics. His experiments were too few to be conclusive, but indicate the correctness of his deduction.

*Muscles.*—According to Charles Livon, salicylic acid has a distinct influence upon the muscle-tissue of the frog, producing a primary increase and secondary decrease of excitability and altering the character of the muscular contractions.

*Circulation.*—There was at one time a belief not only among clinicians, but also physiologists, that salicylic acid even in small doses decreases the arterial pressure. It seems, however, to be established that while toxic doses of salicylic acid do depress arterial pressure, moderate doses exert no such influence; indeed, Danewsky is probably correct in asserting that they increase the arterial pressure by stimulating the vaso-motor centres. The final fall of the arterial pressure is in large part, if not altogether, due to a direct action of the drug upon the heart itself.

E. Maragliano, in a very large number of sphygmographic and sphygmomanometrical studies, found the arterial pressure usually elevated, and never depressed, by therapeutic doses of the drug. In 1879 Hugues Oltremare affirmed that moderate doses of sodium salicylate increased the frequency of the pulse and the arterial pressure, and in this was subsequently confirmed by Danewsky. According to the latter observer, although the force and energy of the cardiac beat are increased by the small dose of the drug, yet the inability of the salicylate to elevate the arterial pressure after section of the spinal cord shows that the main factor in the rise of the blood-pressure is spasm of the blood-vessels due to stimulation of the vaso-motor centres in the medulla. Köhler, Oltremare, and Danewsky have found that after toxic doses the arterial pressure steadily falls, the heart-stroke becoming



weaker and weaker, and finally being extinguished. Köhler, determining that the fall of pressure is not prevented by previous section of the depressors, the vagi, and the cervical cord, logically concludes that it is due to an action upon the heart itself. In Paul Favat's experiments upon the isolated heart of the frog, small doses of salicylic acid had no perceptible influence, although large doses paralyzed the viscus. W. Wiechowski, as the result of an elaborate research, believes that salicylic acid acts specifically upon the brain circulation in causing contraction of the blood-vessels, but that this action is not shared by benzoic acid, by aspirin, or by the oil of gaultheria. He quotes as concurrent with his conclusion the observations of Uthoff, that salicylic acid produces narrowing of the retinal vessels.

*Digestive Tract.*—The indigestion, loss of appetite, and nausea which often interfere with the usefulness of salicylic acid and its compounds are not due to the irritant action of the drug so much as to an influence of the salicylate on the action of the digestive ferments; even when the salicylates are not administered during digestion, it is probable that they are excreted continuously into the stomach and exert their specific action.

According to Kolbe and others, salicylic acid arrests or prevents the action of the non-organized organic ferments. Thus, it will inhibit the action of emulsin upon amygdalin or upon myronic acid, and prevent the development of hydrocyanic acid or of the volatile oil of mustard. Miller found that one per cent. of salicylic acid was sufficient to check the action of ptyalin upon starch; for the same effect ten per cent. of phenol was required. The digestive action of pepsin, outside of the body, was very seriously affected by 0.2 per cent. of salicylic acid in Miller's studies, but in Kolbe's experiments the ingestion of twenty grains a day of the drug had no demonstrable effect.

The belief of many clinicians that the salicylates have a distinct action in stimulating biliary secretion seems to have a solid experimental foundation in the researches of H. Moreigne, in the experiments made upon animals by various observers, and in the observations of William Bain and of Pfaff and Balch upon human beings suffering from biliary fistula. (See bottom p. 514.)

*Nutrition.*—The experiments of Haig, of S. Wolfsohn, of C. Virchow, of E. G. Salomé, of M. Kumagawa, of F. Tausk and B. Vas, of Bohland, and of F. G. Goodbody, which have been made upon various animals and upon healthy men are so numerous and concordant in their relations as to prove, despite the contrary result of Wiley, that in the normal man or animal salicylic acid and its preparations *increase to a very great extent the elimination of urea and uric acid*. In the experiments of Kumagawa, the uric acid was increased in the healthy dog from thirty to seventy-four per cent. There was also marked increase in the elimination of sulphur compounds, although the relation between the elimination of nitrogen and sulphur, which in the normal animal is fixed, was distinctly disturbed.

The question whether the increased elimination of urea and uric acid, produced by the salicylic acid, is due to an increased formation of these substances, or is simply the outcome of increased activity in elimination, cannot at present be answered positively. Schreiber and Zandy would seem to be correct in believing that there is increased formation of urea, but the experiments of Lecorché and Salamon

indicate that in rheumatism the action of the acid is rather in favoring elimination than increasing formation. Thus, these observers found that in acute rheumatism there is under the influence of salicylates an increase both of urea and uric acid, usually lasting three or four days, and then followed by a lessening of the excretion which in many cases carries the elimination of these substances below the normal. If the theory of increased formation of urea and uric acid under the influence of salicylic acid be adopted, the question naturally arises as to the method in which the drug acts in producing the increased formation. Concerning this we have no light at all.

Closely connected with the subject of the action of the salicylates upon nutrition is that of their influence upon temperature. Both in the normal man and in the lower animals, except in rare cases, even the largest therapeutic doses of the salicylates do not lower the bodily temperature (Fürbringer, Gedl, Danewsky, and Sée). It is probable, however, that salicylic acid, like quinine, has, in non-toxic doses, some control over thermogenesis in health. Thus, in one or two experiments upon himself, North found that the acid exerted a decided influence in preventing the rise of bodily temperature normally caused by exercise.

In fever the antipyretic action of the salicylates is very pronounced; usually in about fifteen minutes after the administration of the drug a profuse sweat appears, which is soon followed by a fall of temperature that, according to Justi, reaches its maximum in about six hours.\*

The sweating is profuse and exhausting, amounting, according to Ewald, not rarely to seven hundred and fifty grammes. The perspiration can scarcely be the chief factor in the reduction of temperature, as there appears to be no relation between its amount and the degree of the fall, and it usually ceases before the latter reaches its maximum.

In what way the fall of temperature is produced we have at present no knowledge, since in the only experiments upon the subject—those of Hobart A. Hare,—the doses employed were not sufficient to give positive results.

Especially was this true in the experiments made upon animals suffering from fever. Indeed, there was not in those animals any fall of bodily temperature under the influence of the salicylic acid administered. To attempt to reason from the results reached as to the method of the action of salicylic acid when it does cause fall in bodily temperature seems futile.

**SUMMARY.**—Salicylic acid, and to a less degree the salicylates, are irritant to the mucous membranes, though it is probable that the disorder of digestion produced by the acid and its salts is chiefly due to their inhibiting the activity of the digestive ferments. Salicylic acid is readily absorbed and probably circulates in the blood as a sodium or other salicylate; it is eliminated partly unchanged as a salicylate, partly as salicyluric acid, the

\* The statements in regard to the action of salicylic acid on the pulse in fever vary so much as to suggest that when any decided lessening of the cardiac beat does occur, it is dependent upon the fall of temperature. Thus Garcin (*Journ. de Thérap.*, 1876, 25), Oulmont (*Le Progrès Méd.*, 1877, 587), and Moeli (*Deutsches Archiv*, xvii, 592) have all observed the pulse-rate to fall with the fever-heat, while L. Schroeder affirms that after moderate doses the pulse is slackened, after large ones quickened, and Ewald and other observers state that it is usually not affected.

green discoloration of the urine being due to indican, or perhaps to pyrocatechin, which may be an educt from the acid. The elimination both of urea and uric acid is increased by the salicylates. It is probable that this increase is due to some action upon general protoplasmic chemical activities, though it may be that the salicylates increase chiefly the elimination of formed urea and uric acid. In full doses salicylic acid causes symptoms resembling those produced by quinine, but after larger doses there are mydriasis, marked disturbance of respiration, great nervous prostration, delirium, dyspnoea, and, if the dose has been large enough, death by respiratory paralysis. Moderate therapeutic doses appear to have no powerful influence upon the circulation, such physiological evidence as we have indicating that they increase arterial pressure somewhat by exciting the vaso-motor centre and directly increasing the cardiac force. In overdoses salicylic acid causes fall of the arterial pressure, partly by a direct action upon the heart. Our knowledge of the action of the acid upon the nervous system is very imperfect, but it seems to be a depressant of the motor nervous centres. Moderate doses increase the frequency of the respiration, probably in part by an action upon the peripheral pneumogastrics, but chiefly by a direct influence upon the respiratory centre. Toxic doses paralyze the respiratory centre. The action of salicylic acid upon the temperature of normal man is slight and inconstant, unless toxic doses be given; in fever its antipyretic influence is pronounced, but we have no exact knowledge as to the method.

**Therapeutics.**—The salicylates were originally introduced by E. Butt for the purpose of reducing temperature in typhoid and other fevers, but have been superseded by various agents which are not only more effective but more sure and less disagreeable in their action. In 1876 Stricker, of Berlin, using salicylic acid as an antipyretic in acute rheumatism, discovered the extraordinary antirheumatic influence of the salicylates, which have come to be the standard remedy in all forms of rheumatism. Of all known agents the salicylates are possessed of the most power for good in *acute inflammatory rheumatism*, *subacute or muscular rheumatism*, in *rheumatic neuritis* and other irregular forms of rheumatism, and are often temporarily of great service even in *chronic rheumatism*. In *gout* the powers of the salicylates for good are much less than they are in rheumatic diseases, but in all of the irregular forms of gouty diseases a salicylate should be tried, and will often be found to be of temporary service; they usually combine well with colchicum. Clinical experience has demonstrated that in these various conditions the salicylates seem to be palliative rather than curative; in other words, that they for the present modify and overcome the rheumatic symptoms, but that they exert no permanent influence upon the diathesis which is the basis of the disease. In septic simulations of rheumatism, such as gonorrhœal rheumatism, and in rheumatoid arthritis, the salicylates are rarely of any service.



In *rheumatic angina* and in *quinsy*, which seems to have some relation to the rheumatic diathesis, the salicylates often do good; they are, however, of no value in *diphtheria*. At one time the salicylates were used to a considerable extent in *chronic cystitis* and *chronic pyelitis* for their influence upon the inflamed mucous membrane, but at present are rarely employed.

The salicylates have been used to some extent as antiperiodics, but the general drift of experience coincides with that of Helley, who found salicylic acid to fail in severe cases of malaria, and to require a longer time for the cure of mild cases than does quinine.

As alternative diuretics the salicylates have been commended by Armin Huber and other clinicians in the treatment of *acute* and *chronic pleurisy* with watery effusions. They have been highly commended in *diabetes mellitus* by Williamson and others.

*Ophthalmic Uses.\**—The salicylates are of the greatest value in the treatment of *iritis*, *iridocyclitis*, *iridochoroiditis*, and, in general terms, in *uveitis*. They relieve the pain of acute and sub-acute *glaucoma*, and even cures of the so-called *malignant glaucoma* by them have been reported by Harry Friedenwald, while the course of *sympathetic ophthalmia* is favorably influenced by them.

Naturally the promptest results are obtained in rheumatic cases, but in inflammations of the uveal tract, not of rheumatic origin, they frequently relieve pain and aid in the bringing about of the subsidence of the inflammation. They are also effective in certain types of interstitial and other forms of *keratitis*, in *herpes* of the cornea, and in traumatisms of the eyeball, associated with congestion or inflammation of the iris and ciliary bodies.

In order to get the proper results from the salicylates in diseases of the eye it is essential that they be used in sufficient dose. Gifford believes that most patients are able to take daily one grain of sodium salicylate for each pound of weight, without inconvenience. Thus, a man weighing 150 pounds should tolerate ten fifteen-grain doses, given one and a half hours apart.

From a very large experience I am sure of the value of the salicylates in these diseases of the eye, but I have not found it ordinarily necessary to use the massive doses advocated by Gifford. His plan is to give during the first twenty-four hours eighty to one hundred grains; sixty grains during the next twenty-four hours, and then gradually decrease the dose, administering with the salicylates small doses of brandy if depression be feared. In my own opinion such doses should be reserved for the serious types of ocular inflammations, especially sympathetic ophthalmia, acute glaucoma, and iridocyclitis. In all cases the local treatment of the disease must not be neglected.

Attempts have been made to administer the drug subconjunctivally, but both in man and in rabbits such use is apt to produce local necrosis, and in the writer's experiments upon animals there

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\* Written by Prof. George E. de Schweinitz.

has been caused a degree of local irritation which has made him unwilling to make trial of the method upon human beings. The experiments of Fromaget and Laffay indicate that the solution for subconjunctival medication should never be stronger than five per cent. So far as I am aware intravitreous injections of sodium salicylate have not been practised on human beings; although the experiments of Schoeler show that in the rabbits they have the power to check metastatic iridocyclitis.

The studies of Harold Gifford to determine the manner in which the salicylates act in diseases of the eye have not led to definite result. As Gifford points out, in order for the sodium salicylate to check the growth of the ordinary white and yellow pus cocci it requires a solution of from 1:1000 to 1:500, so that the bactericidal influence of the drug can scarcely be a potent factor in its action. It has been suggested that the salicylate may cause a local depletion in the inflamed area, the arterioles of which have been dilated *ad maximum* by the bacterial toxins by producing a general capillary dilatation. Also, that the diaphoresis caused by the drug is an important factor in its efficiency; but it must be remembered that other drugs which produce capillary dilatation and free sweating are of little value in ocular inflammation.

*Use as an Antiseptic.*—Salicylic acid was originally brought to the notice of the profession on account of its inhibitory influence on putrefaction. Kolbe found that 0.04 per cent. had great influence in preventing souring of milk. Buchholz states that 0.15 per cent. is sufficient to prevent the development of bacteria in ordinary organic mixtures, and that the influence of 0.005 per cent. is plainly visible; 0.3 to 0.4 per cent. of the acid killed bacteria in vigorous growth. H. C. Wood, Jr., has shown that neutralization of the acid with either sodium or strontium very greatly reduces its germicidal power. In the preservation of urine, Meyer and Kolbe found that one part of salicylic acid to two thousand parts of urine was sufficient to prevent putrefaction.

There can be no doubt that salicylic acid is capable of accomplishing much in antiseptic surgery, but it is at present rarely used.

Salicylic acid has been used to a considerable extent in the preparation of beer and wine, and for the preservation of various articles of food. On February 7, 1881, the French government interdicted this use, and in 1885 a commission appointed by the Academy of Medicine of Paris, at the suggestion of the Minister of Agriculture, reported that it is proved that the prolonged employment of even very small amounts of salicylic acid is dangerous, and that in susceptible individuals, and especially in aged persons, it is apt to cause disorder of digestion and renal disease.

Locally, salicylic acid is a distinct irritant. In the experiments of Hodara its prolonged contact with the skin caused swelling of the epidermis, followed after a time by desquamation or exfoliation, the cast-off flakes having a thickness in direct proportion to the strength

of the preparation used. When the application was continued for some days oedema and necrosis of the epithelium resulted. It is also much used by dermatologists in various *skin diseases* when there is pronounced thickening of the epidermis.

In 1875 Hirt called attention to the irritation of the pulmonic mucous membrane in workmen engaged in the manufacture of salicylic acid; and various specialists have employed it as a local remedy in the treatment of chronic laryngeal and pulmonic inflammations.

**Administration.**—The salicylates have been used in rheumatism according to two methods. By one, they are given continuously in moderate dose; by the other, they are administered in very large dose up to the production of cinchonism, then temporarily withdrawn, then readministered, and so on until the desired effect has been reached. When the symptoms are acute the alternative method of administration is better than the attempt to make the continuous prolonged effect; and even in subacute cases of the disease this plan of medication is often singularly effective.

On account of the tendency to interfere with digestion the salicylates should be administered about two hours after meals, so as to get the minimum gastric effect at the time when gastric digestion is at its height. Owing to the irritant action of salicylic acid some of its preparations are at present always preferred.

When, however, salicylates are to be employed in large doses, they must be given in solution, and should, unless under very exceptional circumstances, be administered in milk. When large doses of the salicylates are to be taken, strychnine and often tincture of digitalis may be given with them to overcome their depressing effects. The Oil of Gaultheria is as prompt in its influence as is the ammonium salicylate, and may often be combined with it or used by itself.

The maximum daily dose of the salicylates may be set down as one hundred grains (6.5 Gm.), though in rare cases only is it well to give over seventy-five grains (5 Gm.), and usually less will suffice. In subacute cases thirty grains (2 Gm.) a day is an average dose. The occurrence of tinnitus aurium is an evidence of systemic intoxication, and should be the signal for the lessening of the dose.

**Toxicology.**—When salicylic acid is given to man in doses just sufficient to manifest its presence, symptoms closely resembling cinchonism result. These are fulness of the head, with roaring and buzzing in the ears. After larger doses, to these symptoms are added distress in the head, or positive headache, disturbances of hearing and vision (deafness, amblyopia, partial blindness), and excessive sweating. According to Reiss, decided fall of temperature without alteration of the pulse also occurs; but this is denied by other observers.

The urine may be increased, diminished, or in normal amount, during the administration of salicylic acid. After toxic doses it becomes albuminous, and Sée reports a case in which the renal irritation was so severe as to give rise to hematuria.



In salicylic-acid-poisoning, along with an intensification of the symptoms already mentioned, there are ptosis, deafness, strabismus, mydriasis, disturbance of respiration, excessive restlessness passing into delirium, slow laboring pulse, leucocytosis, olive-green urine, and involuntary evacuations. In some cases the temperature has remained about normal, but in others has approached that of collapse. The respiration appears to be almost characteristic: it is both quickened and deepened. In some cases the dyspnoea has been extreme, and given rise to the most violent respiratory efforts. Various local evidences of vaso-motor weakness may supervene, such as rapidly appearing bed-sores at points subjected to pressure, and transitory dark-colored maculæ on various parts of the body.\*

In several cases death has probably been produced by the acid. The most conclusive case is that of H. Quinke. The chief post-mortem changes were a breaking down of the blood, congestion of most of the viscera, and ecchymoses in the serous membranes.†

In rare instances even the therapeutic use of salicylic acid has produced severe skin eruptions. The form has been sometimes like the eruptive of urticaria, in other cases it has been exanthematous, bullatous, or it has even been purpuric and gangrenous.‡

In some cases of salicylic-acid-poisoning the mental disturbance has been prolonged a week or more. It is stated that upon drunkards the acid acts very unfavorably, violent delirium being a common and early symptom of its influence. There are also some persons whose idiosyncrasies are such that mental disturbance is produced even by moderate doses of the acid. In some cases the delirium is cheerful, in other it is melancholic in type. In the mildest form it is manifested only by a tendency to dream actively and to talk during sleep. In other cases the roaring in the ears soon becomes associated with disturbances of vision, which grow more marked until the patient not only sees objects in false appearances and colors but has absolute illusions. The hallucinations are apt to take the shapes of animals such as are seen in delirium tremens, but there is usually little or no terror, and the troops of images may march to beautiful music. In other cases the delirium amounts to acute mania, with restlessness, violent outcries, and even a fury of fighting (J. Krueg). Mydriasis and amblyopia like that caused by quinine have been noticed in a number of cases, but Gibson and Felkin report excessive myosis, with loss of the light reflexes.

Oil of gaultheria is more irritant than the other salicylates, but is capable of causing all the ordinary symptoms of poisoning by salicylic acid.

\* For cases, consult *Deutsches Archiv f. Klin. Med.*, xix, 319; *Centralbl. f. Chirurgie*, 1877, 278,—four hundred and one grains of sodium salicylate taken in twelve hours; *London Lancet*, 1876, 2, 681; *Berlin Klin. Wochenschrift*, 1876, No. 4, 8; and *Bull. Therap.*, 1877, xcii, 25.

† In the case recorded in the *Virginia Med. Monthly*, June, 1877, forty-eight grains of the acid were taken in four hours. The symptoms were violent vomiting, headache, total unconsciousness, and stertorous breathing. Death occurred forty hours after the first dose. Our belief is that either much more of the acid than forty-eight grains was taken, or, what is more probable, death was from some other cause. (See also *Med. and Surg. Reporter*, 1878.) The case reported by Dixneuf (*Thèse*, Paris, 1878), also that of Empis and Gubler (*Bull. de l'Acad. Med.*, 1877), we have not had opportunity to examine. It is worthy of remark that in the early history of the use of the salicylates disagreeable symptoms appear to have been present much more frequently than of later years, and it is very probable that in many cases such symptoms have been due to the presence of impurities. Thus, *paracresotic acid* has been isolated from commercial salicylic acid by Dunstan. Both it and *orthoacresotic acid* have been found by Charteris to be very fatal poisons to the lower animals, producing general paralysis and death from asphyxia. One grain of orthoacresotic acid and two grains of paracresotic acid caused death in three hours in rabbits weighing two pounds (*Brit. Med. Journ.*, 1891, i.).

‡ *Journ. of Cutaneous and Genito-Urin. Diseases*, 1896; see especially *Deutsch. Med. Wochenschr.*, 1886.

An ounce produced violent gastro-intestinal irritation, followed by convulsions, coma, and death in fifteen hours, Pinkham. In Juvet's case a half-ounce caused death; but the same amount has been recovered from (Gallaher), probably on account of the vomiting induced.

ASPIRIN (*Acetyl-salicylic Acid*) occurs in white, crystalline, insoluble needles, of an agreeable taste, which undergo decomposition in alkaline fluids with the separation of salicylic acid, and are therefore changed by the intestinal fluids.

Although the urine affords evidence of the presence of salicylic acid in half an hour after the ingestion of aspirin, according to Filippi and Bufalini, the excretion of the salicylic acid takes place much more slowly than when sodium salicylate has been taken.

Aspirin is undoubtedly capable of acting physiologically and therapeutically as a salicylate. In full doses it produces cinchonism, and it may cause disturbances of the digestion and the other disagreeable effects of the remedies of the class.\* It is, however, usually better borne than are the older salicylates, and is probably somewhat more continuing in its influence, so that it is especially suitable to the treatment of subacute and chronic cases, in many of which, when the symptoms are not severe, marked benefit may be derived from the exhibition of a single dose of the aspirin at bedtime. Like other salicylates it increases very markedly the elimination of uric acid and other nitrogenous excreta (Singer). It appears, however, to have some peculiarities in its therapeutic influence; according to Liesan, in large dose it acts as a powerful sudorific, and many clinicians are concurrent in the statement that both its analgesic and antipyretic influences are much more marked than is the case with most salicylates. It has been used by various clinicians with asserted good results to depress temperature in *fevers*, and has been highly praised as a means of subduing pain in *migraine*, *neuralgia*, and even in the fulgorant agonies of *locomotor ataxia*.

UNOFFICIAL SALICYLIC ESTERS.—A number of esters of salicylic acid have been proposed as antirheumatics, especially for the local application.

GLYCERINE SALICYLATE (*glycosal*) is a white crystalline powder, sparingly soluble in water, fairly soluble in alcohol, which is recommended to be applied in the form of a twenty-per-cent. alcoholic solution, covered with an impenetrable dressing and left in place for from six to eight hours. Block uses a twenty-per-cent. collodion with asserted success.

AMYL SALICYLATE is a colorless liquid, with a salol-like odor, of which one-half to one fluidrachm may be applied to rheumatic joints and covered with waxed paper.

METHYLOXYMETHYLSALICYLATE is a yellow, clear, fluid with a faint peculiar odor, mixable with oils. It may be applied diluted with nearly equal parts of olive oil; one to three fluidrachms of the mixture applied to the affected part, covered with impervious dressing. The application sometimes produces eruptions of the skin.

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\* A case has been reported by Otto (*D. M. W.*, 1903, xxix.) in which aspirin produced violent general oedematous erythema, affecting also the mucous membranes, with slightly albuminous urine, but no fever and only mild increase in the rapidity of the pulse without irregularity.

**SALOPHEN.** *Acetylparamidophenyl.*—Salophen, which contains 50.9 per cent. of salicylic acid, occurs in white, crystalline, insoluble leaflets, and is said to undergo decomposition in alkaline solution. Siebel states that it yields salicylic acid in the alkaline intestinal juices.

It has been largely used in the treatment of all forms of *rheumatism*, but is especially adapted to the subacute and chronic cases. It is capable of producing cinchonism and other salicylic acid symptoms, but is less likely to disturb the digestion than are the older salicylates. Forty-five to seventy-five grains of it (3-4.85 Gm.) may be given in the course of the day, in divided doses in capsules, or better diffused in milk or water.

### ANTIPYRINE.

*Antipyrine* or *phenyl-dimethyl-pyrazolon*, was discovered by Ludwig Knorr, of Munich, and first experimented with by Filehne, of Erlangen. It is a grayish or reddish-white crystalline powder, of a slightly bitter taste, soluble in thirty parts of ether, in less than one part of water, and also very soluble in alcohol and chloroform.

Antipyrina (Phenazonum) . . . . . 5 to 20 grains (0.3-1.2 Gm.).

**Physiological Action.**—*Local Action.*—The local action of antipyrine is not thoroughly understood. It is somewhat irritant, and it is alleged that it acts with sufficient power upon the sensory nerves to be useful as a practical local anesthetic, especially when applied to the laryngeal or nasal mucous membrane. It is also stated that antipyrine is a very active hemostatic, a forty-per-cent. solution causing, when applied locally, most active contraction of all the small blood-vessels.

Saint-Hilaire affirms that the anesthesia produced by antipyrine is complete and generally lasts from one to two hours; that the sensibility to touch and also to heat and cold is destroyed, the thermal sense returning first; also, that the solution must not be of less strength than thirty per cent., twenty-per-cent. solutions having no anesthetic effect. Huchard and Henocque (quoted by Armand) state that when they cut off the feet of guinea-pigs and put the various stumps into a solution of antipyrine, or tincture of ferric chloride, etc., the bleeding was arrested most quickly by the antipyrine.

*Absorption and Elimination.*—Antipyrine is absorbed with rapidity and is eliminated through the kidneys, partly as antipyrine and partly as a new substance which is, according to Lawrow, a compound of oxyantipyrine with glycuronic acid.

I. I. Hage was unable to find the drug in the sweat or the saliva, but it has been found in minute quantities in the milk of nursing women both by Pinzani, and by Fieux. Armand states that it can be continuously detected in the urine from twenty-five minutes to thirty-six hours after its ingestion, although most of it is eliminated in the first twelve hours. Perret and Givre found that urinary elimination begins in the adult or in the child three-quarters of an hour to an hour after the ingestion, but that the child eliminates the antipyrine more rapidly than the adult. According to Maragliano, the elimination is at its height in four hours, and continues for a day and a half. The urine is sometimes increased, sometimes diminished, in quantity; it is normal in appearance, and never contains albumin or sugar.



The theory, that the liver retains or modifies antipyrine, is made more plausible by the researches of Wera Iwanoff, who finds that the liver-cells of frogs poisoned with antipyrine undergo very pronounced changes in their nuclei and protoplasm. The statements of Iwanoff are especially important in connection with the known effect of antipyrine upon urea elimination. Disturbances of the hepatic function may be at the basis of the inhibitive action of the drug upon urea formation.

*Nervous System.*—In sufficient dose, antipyrine is a paralyzant to both motor and sensory nerves, although in the human being this effect is manifested only after the local application of the drug. It is probable, although not certain, that antipyrine also acts upon the spinal cord primarily as a stimulant, but in larger quantities, secondarily depressing.

The quietness produced by therapeutic doses of antipyrine and the cerebral symptoms of antipyrine-poisoning, show that the drug has a peculiar influence upon the cerebral cortex. Simon and Hock believe that their experiments prove that the special senses are first stimulated and then paralyzed. The convulsions of antipyrine-poisoning are probably in part epileptiform (*i.e.*, of cerebral origin) and in part tetanic (*i.e.*, of spinal origin), though the testimony concerning this matter is contradictory.

According to the observations of Leon Arduin, Demme, Coppola, Simon and Hock, and others, in the frog, in moderate toxic doses (half to one centigramme), it causes convulsions, with opisthotonos, and a very marked increase of reflex activity. In the earlier stages of this condition the animal is cataleptic, and L. Blumeneau affirms that there is a primary stage of quiet with diminished reflex activity. If given in overwhelming amount, antipyrine causes in the frog immediate quiet, muscular relaxation, with loss of reflex activity, deepening into complete paralysis and death. In mammals the chief symptoms of antipyrine-poisoning are ataxy, paraplegia, hurried respiration, convulsions with general rigidity, dilated pupils, unconsciousness, and fall of temperature, ending in death, which seems to be due to failure of respiration.

Blumeneau and Batten and Bokenham state that section of the cord does not prevent the occurrence of the convulsions in the posterior segment of the body; while Coppola and Simon and Hock state that it has such action. Either the first-named observers failed to make complete section or else both cerebral and spinal convulsions are produced by the drug.

Choupe states that the drug even has the power of suspending the strychnic convulsions. If the observation of Blumeneau—that in a frog with the cerebral hemispheres removed antipyrine produced slowness of reflex reaction, which immediately disappeared upon section of the spinal cord high up—be correct, the primary reflex depression is probably cerebral.

There seems to be no doubt that antipyrine *paralyzes both the motor and the sensory nerves.*

Lepine has noticed that if access to a motor nerve be shut off, such nerve, after death from antipyrine, will be distinctly more active in its response to stimuli than is the implicated nerve; while Simon and Hock noted in frogs killed with antipyrine the motor nerves absolutely paralyzed, and have also demonstrated the influence of the drug by bringing it in local contact with an exposed nerve. These latter observers further confirm the earlier work of Coppola, and it seems to be proved that when applied locally, or given internally, antipyrine is a distinct *depressant of the sensory nerve-trunks.* Simon and Hock state that in the beginning of the convulsive stage animals can be operated upon without the use of an anesthetic.

How far the vaso-motor and other nerves connected with the involuntary movements of the body are influenced by antipyrine is at present uncertain, although there is some reason to suspect that the drug acts upon them as it does upon the nerves connected with voluntary life.

According to Batten and Bokenham, when locally applied to the exposed intestine, antipyrine prevents the peristaltic wave which is normally produced by the application of common salt, although it does not check the annular contraction at the point of irritation; an effect which seems explainable only by the supposition that the intestinal nerves and not the intestinal muscles are paralyzed by the drug.

*Muscles.*—According to Devraux-Armand, the muscular stiffness of advanced antipyrine-poisoning, when the poisoning is fatal, passes directly into post-mortem rigidity. Moreover, in Armand's researches the contractions of muscles taken from the body of animals killed with antipyrine were much more powerful and prolonged than were those produced by the same amount of stimulation in the normal muscle.

*Circulation.*—Although the effects of antipyrine on the circulation are of secondary importance, Demme, Arduin, Armand, Henry Casimir, and Cerna and Carter have separately determined by experiment that in moderate doses *antipyrine increases the arterial pressure*, while *toxic doses lower the pressure*. The cause or causes of the rise have not yet been fully determined; it occurs in curarized animals, and is therefore independent of any action of the drug upon the respiratory centre. According to Cerna and Carter, it is not prevented by previous section of the pneumogastric nerves and of the spinal cord, and the pulse-waves accompanying it are of extraordinary size and height. It would appear, therefore, that it is at least in part due to *a direct stimulation of the heart*. Unfortunately, however, the evidence which we have at present is so contradictory that no positive conclusions can be drawn as to the effect of the largest therapeutic dose of antipyrine upon the heart, while in regard to the toxic doses it is more than probable that they directly depress the heart.

Arduin, Demme, Lepine, and Armand all affirm that in the poisoned frog the heart is arrested in diastole, but Coppola states that antipyrine has no influence upon the circulation in the frog, that in many cases after the largest dose the heart is arrested in systole, and that in the Williams apparatus no effect is produced by antipyrine upon the isolated heart unless the dose be enormous. Faval found, however, that while moderate doses have little effect, large doses diminish the frequency and force of the cardiac contractions in the isolated heart of the frog, and finally cause diastolic arrest.

The action of the drug upon the vaso-motor system is at present writing very doubtful. Cerna and Carter affirm that it has no influence upon the blood-vessels, but give no proof of this; and the fact ascertained by Casimir, that the rise of arterial pressure is accompanied by a distinct decrease in the size of such vascular internal organs as the kidneys, indicates that the drug produces a vaso-motor spasm, a view which receives confirmation from the assertion of Arduin, that antipyrine is a powerful local hemostatic. On the other hand, Querrolo (quoted by Armand), employing the plethysmograph of Mosso, found that the arm is increased in size

under the influence of antipyrine, and therefore that the peripheral vessels are dilated, and Casimir affirms that similar dilatation can be seen in the blood-vessels of the ears of rabbits poisoned by antipyrine.

The fall of the arterial pressure is without doubt, at least in part, the result of a depressing influence of the drug upon the heart itself; but if the observation of Bettelheim (quoted by A. Biach), that during the fall of blood-pressure the temperature of the interior of the body notably falls, while that of the exterior correspondingly rises, be correct, vaso-motor paralysis probably is also a factor.

According to the researches of Cerna and Carter, the pulse is usually increased in rate by full doses of antipyrine through a paralytic influence upon the inhibitory nerves, but afterwards becomes decreased in number through the direct action of the drug upon the heart itself.

The peculiar lividity often seen in persons under the influence of antipyrine is probably due to changes in the blood itself. According to Lepine, methemoglobin is largely formed during the poisoning, but Crolas and Hagoumeng failed to detect it. The three observers are in accord in finding that the number of the red corpuscles is not perceptibly affected, even by the continuous exhibition of very large doses.

*Temperature.*—When given in large doses to the normal animal, antipyrine frequently, but not invariably, produces fall in the bodily temperature; in the fevered animal this fall is more marked and more constant. Its cause is not entirely established, but it is probably the result of diminished heat production\* through an influence exerted directly upon the thermogenetic centres. It is certainly independent of any action upon the general circulation, as we have seen the temperature of fevered dogs reduced four or five degrees by antipyrine without change in the arterial pressure.

In seven out of nine experiments made by H. C. Wood, E. T. Reichert, and Hobart A. Hare upon normal animals, there was a decrease in both the production and the dissipation of animal heat. In two experiments both functions were distinctly increased. When tetanic convulsions occur from antipyrine there is a marked rise of the bodily temperature. In both of the calorimetric experiments in which the heat-production was increased, very large doses of antipyrine had been given, and it is believed that the animal suffered convulsions in the calorimeter. In almost all the experiments the decrease of heat-production was very much greater than the decrease of heat-dissipation: it would appear, therefore, that antipyrine in the normal dog primarily lessens heat-production, the reduction of the heat-dissipation probably being the result, at least in part, of the lessened heat-production. In experiments upon dogs in which fever had been produced by injections of pepsin, both heat-production and heat-dissipation were markedly decreased, but usually heat-production was more affected than was heat-dissipation.

The experiments of Destrée and of Engel (quoted by Biach) are, so far as they go, in accord with those just given, while Cerna and Carter found pronounced decrease of heat-production with simultaneous increase of heat-dissipation in dogs fevered by injections of putrid blood. That antipyrine acts through the nervous system is strongly indicated by the influence which it has over fever produced by nerve-lesions.

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\* The experiments of Gottlieb, however, are not consonant with this view; in three experiments hypodermic injections of antipyrine were followed by increased heat-production, with a greater increase of heat-dissipation and consequent fall of temperature. Similar results were also reached in rabbits in which fever had been produced by pricking nerve-centres (*Archiv f. Exper. Path. u. Pharm.*, 1891, xxviii.). These experiments are certainly open to the objection that it is not shown that the changes in heat-dissipation and production which were noted were really produced by the antipyrine, and were not due to the confinement in the calorimeter or to the natural variations in the course of the fever itself; in other words, there were no proper control experiments.



P. J. Martin, R. Gottlieb, and H. Girard are in accord in finding that the rise of temperature which is produced in the rabbit by punctures in the neighborhood of the striate body is lessened or altogether put aside by antipyrine. Martin has further found that heat-production is also lessened under these circumstances. Gottlieb states that Sawadowski has determined that, in the dog whose spinal cord is cut high up, antipyrine no longer reduces the temperature.

The studies which have been made by chemists as to the effects of antipyrine upon the elimination of waste products, taken as a whole, are in accord with the view that antipyrine lessens heat-production. It is indeed true that Chittenden and Cummins were unable to find that antipyrine, either in large or in toxic doses, has any effect upon the elimination of carbonic acid by the animal; but before these results can be considered as established further experimentation is necessary. Again, Armand thought that he had chemically proved that antipyrine increases the elimination of urea; but the original studies of Umbach, who found that large doses of antipyrine very markedly decreased the elimination of urea, have been so abundantly confirmed\* that it would seem that it must be considered established that antipyrine, *both in health and in fever, diminishes the output of the nitrogenous products of tissue-waste.*†

*Antiseptic Influence.*—The influence of antipyrine upon pathogenic micro-organisms and upon fermentation has been elaborately studied by Engel (quoted by Biach), who found that such influence is so exceedingly feeble as to have for practical purposes no existence. On the other hand, Chittenden and Stewart state that antipyrine inhibits, and if present to the amount of three per cent. stops, the digestive action of the acidulated pepsin solution, while Cazeneuve and Visbeck find that one per cent. of antipyrine is sufficient to indefinitely put off putrefaction of the blood. They also confirm the fact that antipyrine is capable of inhibiting the action of ferments like pepsin and diastase. Roux and Rodet find that a four-per-cent. solution is sufficient to very sensibly affect the *Bacillus coli communis*.

**SUMMARY.**—Antipyrine is absorbed rapidly, and eliminated rapidly, at least in part, unchanged. While the ordinary dose of antipyrine produces no distinct symptoms, when in large enough amount the drug causes languor, malaise, cyanosis, depression of the circulation, giddiness, somnolence, epileptiform convulsions, a measles-like exanthema, coma, and collapse. Owing to idiosyncrasy, it provokes in some cases violent urticaria and subdermal inflammation, which may be accompanied by fever and other constitutional disturbances. It is probably a primary stimulant and a secondary depressant of the motor spinal cord. It is certainly a

\* Among the chemists who have reached this conclusion by practical experimentation may be mentioned Wiczowski (quoted by Umbach), Walter, of St. Petersburg (*Therap. Gaz.*, ii.), F. Müller (*Jahresb. für Tierchemie*, xiv.), Ries (quoted by Biach), Albert Robin (*Bull. Acad. Méd.*, 1887, xviii.), and Jacobovitch (*Brit. Med. Journ.*, 1888, ii.). Tausk's (*Schmidt's Jahrb.*, ccxxvi.) failure to get a pronounced effect may have been due to his having used too small doses.

† It would further appear probable that antipyrine alters the normal relation between the various excretitious substances, since Umbach has found that while the urea was markedly diminished, uric acid was scarcely altered; and Robin affirms that in his experiments the elimination of uric acid was even augmented.

paralyzant to both the motor and sensory nerve-trunks, and seems to have also some action upon the muscles themselves. A small dose may moderately increase arterial pressure, probably by directly stimulating the heart and the blood-vessels, although upon these points we have no certain knowledge. The final fall of arterial pressure is due, at least in part, to a direct action upon the heart. In sufficient amount antipyrine causes methemoglobin to appear in the blood. It increases the respiratory rate by a centric action. It probably lessens the production of animal heat by a direct action through the nervous system, independent of any influence upon the circulation, and appears also to stimulate heat-dissipation. Both in health and in fever it diminishes the output of the nitrogenous products of tissue-waste.

**Therapeutic Action.**—In fever cases, about half an hour to an hour after the ingestion of a full antipyretic dose of antipyrine, profuse sweating occurs, and is soon followed by a fall of temperature, which is, however, independent of the diaphoresis.

According to Carl von Noorden, the sweating can be arrested by the use of hypodermic injections of atropine or agaricin without affecting the fall of temperature. Moreover, the sweating is not invariably present, and in dogs, which practically do not sweat, antipyrine is a powerful antipyretic in fever.

According to most authorities, the depression of temperature lasts longer than that caused by some other antipyretics, continuing from two to ten hours. It is accompanied by a reduction of the rate but not usually of the force of the pulse. In some cases the sweating is not profuse, and it is probably under such circumstances that observers have noticed a markedly increased diuresis. Usually the patient is more comfortable under the action of the drug than at other times; sometimes, however, there is distressing vomiting.

Antipyrine may be employed as an antipyretic in almost any disease accompanied by high temperature, such as *pneumonia*, *erysipelas*, and *typhus*, *scarlet*, *yellow*, and *typhoid fevers*, *rheumatism*, etc.; it has also been freely given in the hectic fever of *phthisis*, but various observers state that in such cases it produces so much feebleness and general depression as to forbid its use: nevertheless, our own observation is that when used with caution it often gives great relief. In *typhus fever* it reduces the temperature, but in a number of recorded cases it has induced very serious collapse. It appears to have some specific action in rheumatism, but does not in this respect equal salicylic acid. According to A. Pribram, in *pneumonia* the frequency of the respiration is distinctly lessened by it, but this is probably due simply to the lowering of the bodily temperature. In children it has been used with asserted good results by a number of clinicians, and it appears to be especially useful in the pneumonia and bronchitis of the young.

The second indication for the meeting of which antipyrine is sometimes used with success is the *relief of motor disturbance*. Over the minor spasmodic conditions of *hysterical* origin, over *chorea*, etc.,

antipyrine has a certain amount of power. In 1888 Sonnenberger commended it very highly in *whooping-cough*, stating that if given at regular intervals it greatly lessens the number of paroxysms, or even aborts the disease; and further clinical experience seems to show that the drug has real value. M. A. Choupe states that antipyrine has great power in relieving uterine pains after parturition or in *dysmenorrhœa*, and that if it be given during labor along with ergot it allows the contractions to go on, but renders them painless. In more severe spasmodic disorders antipyrine sometimes does good. It is certainly worthy of trial in *tetanus*, especially when the temperature is high. It may be given in *epilepsy* with some hope of success, since its influence in preventing the return of convulsions is sometimes extraordinary, although in the great majority of cases it fails entirely. We have studied it in a large number of cases, but are unable to point out any indications which will warrant in an individual case an *a priori* opinion that antipyrine will do good. The only method is that of trial. Not less than forty grains (2.6 Gm.) a day should be given, and if, after a time, no cyanosis or muscular weakness mark the physiological action of the drug, and the convulsions still recur, the dose should be increased up to the physiological limit. The combination of antipyrine with ammonium bromide affords much better results than either drug alone, and it has become with us a routine practice to prescribe in epilepsy a mixture of ammonium and strontium bromide with antipyrine. We have given to a large number of cases fifteen grains (1 Gm.) daily of the antipyrine in this combination for many months, and even for years, without cumulative action or perceptible effect upon the general nutrition or the general nerve functions, except that in some cases, probably by disturbance of thermogenesis, a condition of such intolerance of cold is produced that the drug has to be withdrawn, at least for a time. Antipyrine has been used with alleged success in *laryngismus stridulus*, in *nocturnal emissions*, in *asthma*, and in *urinary incontinence* of children.

The third indication which may sometimes be advantageously met by antipyrine is the *relief of pain*. In April, 1887, Sée announced to the French Academy of Medicine that antipyrine is a powerful analgesic, which when given in doses of from forty-five to ninety grains (3–5.8 Gm.) a day will control almost all forms of pain. Such doses, however, border upon toxic, and are rarely justifiable. Moreover, they are scarcely ever necessary in properly selected cases. Abundant clinical experience has shown that antipyrine for the relief of ordinary inflammatory pains is not reliable, and is in every respect inferior to opium; but that it is a very valuable agent against various nervous pains, sometimes giving much more relief than does opium, and usually causing less disturbance to the system. Especially is it effective in *rheumatic pains* and in *migraine* and other forms of *neuralgia* in which the pain is the outcome of nerve-storm; it will, indeed, often control the pangs of *locomotor ataxia*; we have even seen it abort a *gastric crisis*. Whether it acts by a true analgesic influence,



or whether it simply puts aside the nerve-storm which is the cause of the pain, is entirely unknown. In violent *hemicrania* sleep follows relief; but antipyrine is not a true hypnotic. Antipyrine is stated greatly to increase the analgesic effects of morphine, and is itself, in headache at least, made much more effective by caffeine.

Antipyrine has also been used in various disorders not included under the indications already given, often without sufficient reason.

M. H. Feeny reports *subacute Bright's disease* cured by it; Clement, that it is of value in bringing about absorption of *pleuritic effusions*. Both in *diabetes mellitus* and *diabetes insipidus* it has been used with asserted good results. Saint-Phillippe commends it highly in *infantile diarrhæa* with indigestion and pain. Salemi affirms that it is an active practical *antigalactagogue*, and in this has been confirmed by Ryan-Tennison and by Guibert.

**Administration.**—Antipyrine may be administered hypodermically, by the mouth, or by the rectum. The dose for a child of one or two years of age may be set down as two to three grains (0.13–0.2 Gm.); for a child five years old, three to seven grains (0.2–0.46 Gm.); for the adult the dose should not exceed twenty grains (1.3 Gm.), and ten grains (0.6 Gm.) are usually sufficient, in fever cases, repeated every one or two hours until forty grains (2.6 Gm.) are given, or sweating comes on, or the temperature falls.

**Hypodermic Use.**—Antipyrine has been used to a considerable extent hypodermically for the relief of pain, and in neuralgias and nerve-pains good can sometimes be achieved by its local influence. The burning pain produced by the injection of a thirty-per-cent. solution usually lasts only a few minutes, and is not followed by local inflammation. Verneuil, however, has reported partial gangrene of the foot following and apparently produced by a hypodermic injection of antipyrine for the relief of sciatic neuritis.

**Toxicology.**—When given to the normal man in doses of from ten to twenty grains, antipyrine produces usually no distinct symptoms. If, however, it be administered in a larger dose, and especially if it be given in the continuous dose, so as to accumulate in the system, it causes languor, malaise, and a peculiar cyanotic pallor of the face, with failure of the pulse. Vomiting sometimes occurs. The symptoms which have in a number of cases followed large doses are very curious, and some of them difficult of explanation. Prominent among these symptoms is an eruption on the skin, which may occur without constitutional disturbance, but is often accompanied thereby. In its most typical form it consists of small, reddish, irregularly circular spots, resembling somewhat those of measles, and arranged in patches separated by sound skin. The red color usually disappears on pressure, leaving a brown pigmentation, which also comes into view during the fading of the exanthem, and ordinarily continues five or six days. In some cases the eruption is erythematous; not rarely it resembles an urticaria in which the white wheals may be made very prominent by a wide-spread, deep crimson blush.

In a case reported by Spitz the whole surface of the body was covered with bullae, which, becoming confluent, involved the skin in a universal desquamative inflammation. Very frequently the antipyrine rash is accompanied by wide-spread œdema, which may be most pronounced in the extremities, but is especially prone to involve the face, causing great swelling, and even closure of the eyes. The mucous membranes may share in the irritation. Violent catarrhal conjunctivitis is not very rare, while coryza and laryngitis have been noticed.\*

The marked rise of temperature and disturbance of the circulation which often accompany the antipyrine eruption are probably due to the irritation of the skin and the subdermal tissue, since, when the antipyretic eruption takes the form of an urticaria, the itching, sighing, hysterical unrest, and dyspnoea, which are apt to accompany urticarias not due to antipyrine, have been very pronounced.

In a number of cases of antipyrine-poisoning there have been violent nervous symptoms, which seem to be a direct outcome of the action of the poison. The vomiting, which is sometimes accompanied by abdominal pain, may be looked on as an evidence of local irritation; but this is hardly the case with giddiness, somnolence deepening into coma and passing into profound stertorous unconsciousness, with dilatation of the pupils and epileptiform convulsions,—all of which have been noted. The unrest, excitement, and violent tremblings not rarely seen seem also to be directly produced by the drug. H. M. Briggs reports blackish urine with albumin and blood-corpuscles in antipyrine-poisoning.

As illustrative of the symptoms of unusual forms of antipyrine-poisoning may be cited the case reported by F. Spitzer, in which a man, aged twenty-four, shortly after taking one hundred and twenty grains of antipyrine during an hour, complained of violent pain in the belly, and vomited freely; an hour later he was found in a condition of great excitement, screaming, champing his teeth, with a red face, much swollen conjunctiva, and cold extremities; the pulse was 108 per minute, rhythmical, with strong heart-impulse; the respiration 38. There was precordial anguish, pain in the stomach, and marked tremors, with exaggeration of the tendon-reflexes. Fifteen hours after the poisoning he was seized with a sudden chill, with marked cardiac failure, from which, however, he recovered.

In another group of cases collapse and cyanosis have been prominent symptoms. It seems necessary, however, to point out that these symptoms in a large proportion of recorded cases seem to have been due to constitutional peculiarities of the individual rather than to the use of very large doses of antipyrine, and they are rarely attended by danger to life. Thus, E. W. Young reports a serious poisoning by six grains of antipyrine. Theo. Schwabe reports a case in which fifteen grains of antipyrine, given to a young woman for neuralgia, produced violent poisoning with collapse, complete amaurosis, cyanosis, urticaria, etc. In typhoid and other fevers, fatal depression has been produced not infrequently, by doses of antipyrine that were not larger than have frequently been used without evil results. Thus, in Barrs's case, thirty-five grains of antipyrine were given to a puerperal woman with a temperature of 103.6° F., and followed in three hours by half the quantity, after which the temperature sank to 98° F., and, in spite of stimulation, death occurred thirty-two hours later. Our knowledge of the physiological action of antipyrine seems to negative the supposition that the depression in these fever cases is due to any direct action upon the heart or other vital organ. Heat is a stimulant to function, and it may be that the cause of the col-

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\*For cases, see *London Lancet*, 1881, i.; *British Med. Journ.*, 1888, i.; also 1892, i.

lapse is the sudden fall of bodily temperature in a person whose nervous system is excessively enfeebled by a fever of typhoid nature.

**ACETOPYRINE.** *Antipyrinæ Acetosalicylas*.—This occurs as a white crystalline powder, having an odor resembling acetic acid; sparingly soluble in cold, but freely in warm water; freely soluble in alcohol, chloroform, and in warm toluol, less so in ether and in petroleum-ether.

It was originally introduced into medicine by Winterberg and Braun as combining the activities of antipyrine and salicylic acid, into which substances, according to W. Meitner, it is broken up in the stomach; the aspirine undergoing further decomposition in the intestines.

Acetopyrine has been much used as an analgesic in *migraine*, *sciatica*, *neuritis*, and also as an antipyretic in *typhoid* and other *low fevers*. Also as an antirheumatic of especial value in subacute and chronic cases. Its physiological and therapeutic activities are probably those of its constituents. It may be given in doses of five to ten grains (0.3–0.6 Gm.) in capsules, or suspended in water, and repeated up to thirty grains (2 Gm.) in the twenty-four hours when necessary. In fevers two doses may be given two hours apart about the time of the exacerbation.

### ACETANILIDE.

*Acetanilide*, *antifebrin*, or *phenylacetamide*, is an aniline in which one atom of hydrogen has been replaced by the radical acetyl; or it may be considered as an ammonia in which one atom of hydrogen is replaced by phenol and another atom by acetyl. It is a white, crystalline substance, entirely without odor, having a bitter, mildly piquant taste. It is soluble, in one hundred and seventy-nine parts of water and in two and a half parts of alcohol.

#### Official Preparations:

Acetanilidum.....	3 to 6 grains (0.2–0.4 Gm.).
Pulvis Acetanilidi Compositum (Acetanilide 7, Caffeine 1, Sodium Bicarbonate 2).....	5 to 10 grains (0.3–0.6 Gm.).

**Physiological Action.**—*Local Action.*—According to the experiments of L. Frothingham and J. H. Pratt, acetanilide is distinctly antagonistic to disease germs, scarcely killing them, but markedly inhibiting their growth. Applied in the form of powder to a wound or mucous membrane, it acts as a stimulant or feeble irritant, a desiccant, and probably also as an analgesic.

*Absorption and Elimination.*—Absorbed into the blood by some unknown method, acetanilide is in great part or altogether converted into the paramidophenol sulphate,\* and as such escapes from the kidney. It is probable that it breaks up in the organism into acetic acid and aniline, and that the aniline is then oxidized into paramidophenol, which unites with sulphuric acid.†

\* In an elaborate research on various drugs of the aniline group (*Deutsch. Med. Wochens.*, 1895, xxi.) it was found that those substances which produced in the organism *paramidophenol* or *paracetamidophenol* were active, while those which made *ethyl-acetamidophenol* were not active.

† The changes which occur in antifebrin in the system have led to the theory that its medical virtues are dependent upon the liberation of aniline in the blood. The symptoms produced by antifebrin are certainly similar to those caused by aniline. Thus, Herzfel states that in a case of aniline-poisoning the symptoms were colossal cyanosis, sweating, vomiting, tinnitus aurium, dyspnoea, fixedness of pupils, disturbance of sensibility, and a temperature-fall of 5.3° C., accompanied by a marked decrease in the coloring-matter of the blood and of the number of red blood-corpuscles.



Cahn and Hepp, however, affirm that acetanilide escapes finally with the urine in great part unaltered, and that only a small portion of it is converted into aniline and acetic acid; but Müller as well as Pavai Vajna and Kumagawa state that antifebrin cannot be found in the urine, and consequently that it undergoes entire decomposition. Jaffe and Hilbert found that in dogs acetanilid passes off chiefly as o-oxy-carbonol and as paramidophenol, both united with glyco-uronic and sulphuric acids; in rabbits, chiefly as paramidophenol, paired with the acids. It is probable that the proportion of antifebrin which is decomposed varies with the size of the dose and the condition of the system.

**Physiological Action.**—When given to persons suffering from fever in doses of ten grains (0.65 Gm.) acetanilide usually produces in about an hour fall of temperature, which reaches its maximum in two or three hours and may continue from six to seven hours. Usually, but not always, the fall of temperature is accompanied by a profuse sweating, which is generally described by clinicians as being less than that produced by corresponding doses of antipyrine. The fall of temperature is not dependent upon sweating, since it sometimes occurs without the sweating, and G. Pavai Vajna finds that the sweating can be arrested in great part by atropine without interfering with the thermic action of the drug. In rare cases the lowering of the bodily temperature has been coincident with the occurrence of collapse.

The only information we have concerning the method by which acetanilide lowers bodily temperature is furnished by the experiments of H. A. Hare and E. M. Evans. It is not sufficient for a positive conclusion, but indicates that in fevered animals *acetanilide produces a fall of the temperature by decreasing heat-production.*

In fifteen experiments upon normal animals, which in nearly all cases were allowed to run free, Hare obtained a distinct fall of temperature from acetanilide,—a result confirmed by Evans, but not in accord with the results of Cahn and Hepp, who found that antifebrin had not a constant influence upon the temperature of the normal animal. Hare, employing the calorimeter of H. C. Wood, found that in the normal animal heat-dissipation and heat-production were variously affected, in some cases being notably increased, in other cases notably decreased, and in others not distinctly altered. Evans, employing the D'Arsonval calorimeter, also reached various results. In eleven experiments heat-dissipation was decreased nine times, while heat-production was increased four times and decreased five times. In examining the records of the calorimetric experiments made by Hare and Evans on the normal animal, we find that not only did the rectal temperature *not fall* under the influence of antifebrin, but in nearly every instance there was a very distinct rise, amounting in some cases to over a degree. It is evident, therefore, that these experiments cannot be used to explain how antifebrin reduces temperature when it does cause a fall. The attempt to reason how a certain result is produced by a remedy from experiments in which that result was not produced is necessarily futile.

In Hare's experiments, made upon dogs, in which fever was caused by the injection of pepsin, acetanilide failed to produce any constant fall of the bodily temperature, probably because the dose was not large enough. In the calorimetric studies heat-production was usually decreased, but sometimes it was increased,—an assertion which is also true of heat-dissipation. These experiments must likewise be laid aside, because there was no fall of temperature caused by the antifebrin. In Evans's experiments with fever produced by the injection of albumose, the antifebrin nearly always caused a distinct reduction of temperature. In the calorimetric studies the results obtained were constant, there being in each of the six

consecutive experiments a decrease in both the hourly heat-dissipation and the hourly heat-production, the amount of decrease seemingly bearing some relation to the fall of temperature. It is plain that a decrease of heat-dissipation would have a natural tendency to elevate bodily temperature, and therefore the fall of temperature must have been due to the decrease of the production, which in turn gave rise to the decrease in the heat-dissipation.

*Nervous System.*—The cause of the convulsions of acetanilide-poisoning does not seem to have been determined. The coma which is present in the advanced stages of the poisoning indicates that, directly or indirectly, acetanilide affects the cerebral function, but consciousness is stated by experimenters to be preserved at a time when the lower portion of the nervous apparatus is distinctly affected. According to Bokai, antifebrin *paralyzes motor nerve-endings* of the frog's muscles in a manner similar to curare, and when brought in contact with the *muscle* itself for a sufficient length of time destroy its capability of contraction. In the poisoned animal, however, just before death the muscles respond actively, although irritation of motor nerve-trunks fails to elicit response.

*Circulation.*—Usually when acetanilide is given to patients with fever there is a fall in the pulse-rate corresponding to the fall of temperature. The size of the pulse is also reduced, and it may even become thready. Weill has found that, injected into the frog, the drug causes at first an acceleration of the heart's beat, with apparent increase in the force of the impulses, followed after a time by slowing and irregularity of contraction. In the earlier stage the size of the pulse-wave is increased and the respiratory curve is more accentuated; later the pulse-oscillations diminish and become irregular and quickened, and if the dose has been large enough the manometric writing resembles that produced by asphyxia. In the earlier stages of the action there is a slight rise in arterial pressure.

The cyanosis of acetanilide-poisoning has been thought to be due to the formation of methemoglobin and Stewart reports two cases in which the blood had the characteristic chocolate color, although no spectroscopic examination seems to have been made. On the other hand, in cases of poisoning with marked cyanosis, both Freund and Stengel were unable to detect anything abnormal in the blood by spectroscopical examination. The blood changes do not appear to be characteristic; Stewart reports marked reduction of the number of red cells but in one of Stengel's cases the corpuscles were 6,000,000. Herczel states that the red corpuscles do not adhere in rouleaux, that they are somewhat granular, and that, when the drug is given to dogs for a length of time, the blood is less alkaline than normal, and contains in its serum dissolved coloring-matter. According to Lepine and Aubert, the oxygen of the blood is distinctly decreased.

*Nutrition.*—Kumagawa found that while small doses had no definite effect, large doses enormously increased the nitrogenous elimination; but in Pepine's experiments the results varied, there being sometimes an increase and sometimes a diminution, while H. C.

Taylor obtained a slight increase: so that it is impossible at present to say what is the action of the drug upon protoplasmic chemical activity.

According to Kumagawa, acetanilide exerts a strong antiseptic influence upon intestinal changes, decreasing the bacteria in the intestines, and the urinary indican.

**Therapeutics.**—The therapeutic use of acetanilide is exactly parallel to that of antipyrine. Some practitioners prefer it on the ground that it is less liable than is antipyrine to produce collapse, painful skin lesions, or other disagreeable effects, but it is certainly capable of causing fatal acute or chronic poisoning. According to Sembritski it acts very badly on pregnant or nursing women. Lepine affirms that it will relieve not only the fulgurant pains of spinal disease, but also the tremors produced by *multiple sclerosis*, and is often useful in *epilepsy*.

Acetanilide affords a useful surgical dressing, and has the superiority over iodoform of being free from odor, and perhaps of being more analgesic. It is frequently employed with equal amounts of boric acid, finely powdered, in the treatment of minor infected wounds. The powder may be freely used, or an ointment of from ten- to forty-per-cent. strength; in *vaginitis* or *urethritis* a mixture (twenty to forty grains to one fluidounce) with gum-arabic water may be injected. The free external use is not entirely devoid of danger, as cases have been reported of collapse with intense cyanosis and subnormal temperature produced by the surgical use of the drug.\*

**Toxicology.**—The symptoms of *acute poisoning* by acetanilide are vomiting, muscular weakness, cyanosis, coldness of the extremities, subnormal temperature, profuse sweating, disturbances of respiration, fixed dilated pupils, rapid irregular heart action, ending in collapse and cardiac death. In some cases an impaired consciousness has not been present until very late in the poisoning; in others a complete unconsciousness has been a comparatively early symptom. The urine may be dark owing, it is said, to hematoporphyrin (methemoglobin?). Leucocytosis with nucleation of the red blood-corpuscles has been noted.

Occasionally there is an eruption somewhat similar to that commonly produced by antipyrine, which is especially abundant upon the face and forehead, and of a dark red color. Sometimes the eruption resembles that of scarlatina, and there may be much subdermal swelling (Armin Hugher). Mydriasis and deafness, with ringing in the ears, have been noted occasionally. Collapse appears to be less frequent than with antipyrine.\* The experiments of Hobart A. Hare show that at present inexplicable cardiac failure may occur suddenly.

In the experiments of Herczel, the symptoms produced by fifteen to twenty grains in rabbits were loss of the reflexes, tremors deepening into periodic convul-

\* See *Med. and Surg. Rep.*, 1897, lxxvi; *P. M. J.*, Sept. 1901, Herrick and Irons, *J. A. M. A.*, xlv, p. 351.



sive movements, great fall of temperature, frequent, irregular, superficial respiration, retention of urine, coma, and general paralysis, ending, if the dose had been large enough, in death, which could not be prevented by artificial respiration. The heart was arrested in diastole. After the prolonged action of the drug there was fatty degeneration of the heart, liver, and kidneys. Weill noticed, in addition to these symptoms, an anesthesia, which in the later stages of the poisoning was almost complete.

Sixty grains of it are asserted to have caused death, but have been recovered from after the most alarming symptoms. (See Doll, quoted by Biach, also P. Brown.) Marichaux details a case in which four grains (0.26 Gm.) caused in a child collapse, with complete unconsciousness, ending in recovery.

In *chronic poisoning* the most pronounced symptoms are anemia and cyanosis; gastric disturbance, failure of the general nutrition, rapid, feeble heart action, and distinct enlargement, without tenderness, of the spleen have been noticed. There is not only great decrease in the number of the red blood-corpuscles and in the percentage of hemoglobin, but also marked increase in the number of the white blood-cells, with nucleation of the red blood-corpuscles (see Stengel and White).

### ACETPHENETIDIN.

*Acetphenetidin*, or *Phenacetin*, an acetyl derivative of para-amidophenol, crystallizes in tasteless, colorless needles, almost insoluble in water, soluble in alcohol.

Acetphenetidinum—Phenacetin ..... 10 to 20 grains (0.6–1.3 Gm.).

Phenacetin is eliminated by the kidneys, probably entirely altered, phenetidin appearing in the urine. According to Müller, this change must take place after absorption, since both the gastric and pancreatic secretions are without effect on the compound. O. Hinsberg and A. Kast have found that when given to dogs in doses of fifteen-hundredths to two-tenths of a gramme per kilo acetphenetidin has no effect, but in very large doses it causes vomiting, irregular gait, hurried respiration, and somnolence, followed by general cyanosis and discoloration of the blood, due to the formation of methemoglobin.

The therapeutic dose of acetphenetidin produces no symptoms, but the toxic dose is said to cause violent vomiting, great cyanosis, chocolate-colored urine, yellow discoloration of the body, leucocytosis, and death (Krönig). Mahnert states that the muscular weakness produced by acetphenetidin is of spinal origin, and that in massive doses the drug is antagonistic to strychnine, also that both respiration and heart are paralyzed by it. According to the same observer it is chiefly eliminated unchanged; and the urine gives a positive Trommer's reaction, although containing no sugar. Ledoux asserts that in doses of 0.5 gramme per kilo acetphenetidin causes a fall of the blood-pressure; but as he used an alcoholic solution his results are not entirely reliable. H. C. Wood, Jr., and H. B. Wood found that

the drug, given intravenously suspended in water, had absolutely no effect on blood-pressure. Doses of 0.5 gramme per kilo killed by arrest of respiration; which can, perhaps, however, be attributed to the mechanical influence of undissolved particles. Frogs allowed to swim in a saturated aqueous solution of phenacetin in four hours became totally paralyzed, the motor nerves and muscles retaining their irritability. Ott found that phenacetin pronouncedly decreases heat-production without producing distinct alteration of blood-pressure, and, therefore, probably acts as an antipyretic by lessening the heat-production through an influence upon the nervous system. According to Falcone and Gioffredi changes in the cerebral cortical cells can be demonstrated in animals killed with phenacetin.

**Therapeutics.**—Acetphenetidin has been largely used as an antipyretic, and for the relief of pains of such character as antipyrine is employed against. Large amounts of it can apparently be taken without serious result. In a case reported to us by E. C. Wagner, one hundred and twenty grains were taken in twelve hours without the production of any symptoms. The only serious case of poisoning by it, that we know of, is that reported by Hollopeter, in which a woman took twenty-two and a half grains in six hours, producing collapse with marked lividity, great dyspnoea and restlessness, cold perspiration, and slightly dilated pupils, ending in recovery.\*

There can be no doubt of the efficiency of acetphenetidin, and it would appear that it more rarely produces unpleasant symptoms than antipyrine, though urticaria has been noticed after its exhibition (Mahnert). If the statements of Crombie and of Hirschfelder—that it acts more gradually than other antipyretics, and that its influence does not reach its maximum for three or four hours—be correct, acetphenetidin is probably the most valuable of the antipyretics, especially as it seems to be the least poisonous. At present it is probably the most used of its class. Phenacetin is highly commended by M. H. Lee as a local antiseptic dressing.

**PHENOCOLL HYDROCHLORIDE.**—Phenocoll occurs in white needle-like crystals; it is made by the action of glycocoll upon phenetidin. Its hydrochloride is a white, finely crystalline powder, very soluble in water.

**Physiological Action.**—The action of phenocoll upon the animal organism is not very marked, Von Mering having found that twenty-three grains of it will not produce any pronounced symptoms in the rabbit. According to Isaac Ott, the toxic dose produces, in the frog, paralysis of both the motor and sensory functions of the spinal cord, with death from diastolic arrest of the heart; in rabbits, quietude, partial paraplegia, and cyanosis, with acceleration of the respiratory movement and depression of temperature and of the arterial pressure. David Cerna and William S. Carter determined that the influence of phenocoll upon the circulation is exceedingly feeble; enormous doses however caused cardiac depression.

The same investigators affirm that phenocoll has no action upon the blood, but the correctness of this seems to be challenged by the cyanosis which has been noted both in man and in rabbits. In experiments made upon animals with fever, Cerna

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\* Dr. G. Werley in a personal communication has recently given us the account of a fatal case of phenacetin poisoning in a baby of 1 year from 10 grains taken in ten hours.

and Carter found that the fall of temperature produced by phenocoll is due to an enormous reduction of heat-production, heat-dissipation being practically not altered. As the result of some evidently not elaborate chemical studies, P. Balzer states that phenocoll very distinctly increases the nitrogenous elimination: the correctness of this is very doubtful.

Phenocoll is rapidly absorbed and almost as rapidly eliminated. According to Cohnheim, it may be detected in the urine from one to nine hours after its ingestion. It is probably in part oxidized in the system, since the urine after its free administration becomes of a dark, reddish-brown color. It is possible, however, that this color is due to indican and biliary substances, both of which have been found in the urine.

**Therapeutics.**—In 1891 Hertel and Herzog stated that phenocoll rarely, if ever, produces gastro-intestinal irritation or other disagreeable symptoms, that its antipyretic action is quick and never accompanied by any depression, and that the free sweating which is likely to occur with it may readily be prevented by minute doses of atropine. Both Hertel and Herzog assert that phenocoll is a valuable remedy in *acute* and *chronic rheumatism*. In rare instances it produces vomiting, but we have met with no reports of human poisoning by it. The ordinary dose may be set down as twelve to fifteen grains (0.78–1 Gm.), in solution or capsule.

**SALIPYRIN.**—*Antipyrine Salicylate* is a white, coarsely crystalline, odorless, slightly sweetish powder, readily soluble in alcohol. It is commended by Guttman and Kollmann as an active antipyretic and antirheumatic, which rarely produces toxic symptoms, although an eruption resembling that of antipyrine has been noted; the color of the urine is not affected, but tests show the presence of a salicylate. Kollmann states that it sometimes vomits, and that the daily dose should never exceed forty-five grains (2.9 Gm.), and should always be less than this in the beginning, as some individuals are intolerant of it. Salipyrin has been used to a considerable extent in all forms of *rheumatism*, in *influenza*, in various fevers, in *migraine*, and in the whole class of diseases in which its component constituents have been found to be useful; also locally in *coryza*. The usual dose is from seven to fifteen grains (0.45–1 Gm.), in capsule or tablet, repeated every three or four hours, but some clinicians prefer a single large dose of forty-five grains (2.9 Gm.).

**PYRAMIDON.**—*Dimethylamidophenyl-dimethylpyrazolon.*—This is a yellowish-white, crystalline, almost tasteless powder, soluble in ten per cent. of water. It was introduced by Filehne as a remedy having an action similar to that of antipyrine. It appears to be absorbed readily, and, according to M. Jaffe, is in part eliminated unchanged in the urine, in part converted into the red substance, *rubaronic acid*, and in part changed into a substance which is colored deep-blue by ferric chloride, and is, probably, *antipyrilurea*. Its general physiological activities have not been worked out, but G. Ssadowski\* is said to have experimentally determined that it has a powerful action upon the heart and blood-vessels, increasing the arterial tension, so that in cases of tuberculosis of the lungs with already heightened arterial pressure, it may produce hemoptysis, and is, therefore, contraindicated.

Pyramidon has been used to a considerable extent as an antipyretic and as an analgesic. The reports as to its value as an antipyretic in *typhoid* and other low fevers are somewhat contradictory, various clinicians having expressed strong sentiments in its favor, claiming that though it acts more slowly its influence continues much longer than does that of the older antipyretics. Other observers assert that it is more prone than are antipyrine and acetphenetidin to produce excessive sweating and collapse. It has been especially praised in *migraine*, *neuralgia*, and all the pains of the character for which acetphenetidin and antipyrine have been previously used. According to Roth, pyramidon is a useful drug in *acute rheumatism*, though of little value in chronic cases. Albrecht has found it of value in *asthma*.

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\* Ssadowski (*Russkij Wratsch*, 1902, No. 18). We have not seen the original paper, nor yet a satisfactory abstract.



The dose is twelve grains (0.78 Gm.) dissolved in water or taken in capsules, and may, when it is necessary, be repeated up to thirty-six grains (2.3 Gm.) in the twenty-four hours.

Three compounds of pyramidon have been put upon the market, the *camphorate*, the *bicamphorate*, and the *salicylate*. It is affirmed that the presence of camphoric acid markedly lessens the tendency of pyramidon to produce sweating without interfering with its antipyretic action. In the bicamphorate the anhydrotic influence is so great that the drug has been strongly recommended in the *night sweats* in phthisis.

Pyramidon salicylate appears to be inferior in the treatment of *rheumatism* to the older salicylates, though it may be employed in subacute and chronic cases in times of excessive pain. The dose of any one of these preparations is seven and a half to twelve grains (0.5-0.78 Gm.), repeated as necessary. In *tuberculosis*, with excessive sweating, it is advised to give two doses a day of eight grains (0.5 Gm.) each.

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## CLASS II.—LOCAL REMEDIES.

### FAMILY I.—STOMACHICS.

STOMACHICS are drugs which especially affect the mucous membrane and other coats of the gastro-intestinal tract so as to increase functional activity. A *simple bitter* is a substance of vegetable origin and of a bitter taste, which has no influence upon the general system, but markedly affects the stomach as a stimulant. Borissow found that the introduction of tincture of gentian into the mouth, in conjunction with the presentation of food, produced a greater flow of gastric secretion than did the food alone. He believes that this action is a reflex one, depending on the bitter taste. Simple bitters probably influence, however, not only the peptic glands but also the muscular fibres, since Paul Terray found that the movements of the excised stomachs of dogs, kept in a warm salt solution, were increased in the order of naming by extract of gentian, cetrarin, condurangin, extract of taraxacum, quinine, and extract of quassia. Cetrarin was remarkable for its influence upon the intestinal movements. Although simple bitters may, by increasing the amount of food taken, affect the general nutrition of the body, they are essentially locally acting drugs. Probably all bitter vegetable substances are stimulants to the gastric mucous membrane, but in many of them, as in morphine and strophanthin, such power is overshadowed by other inherent properties. Some of these active bitter vegetable substances are indeed employed on account of their influence upon the alimentary tract, notably quinine and strychnine, but in others of them, like morphine, the local is entirely swallowed up in the general influence. By virtue of their irritant action the simple bitters produce, when in overdose, nausea, and may even cause active irritation of the gastro-mucous membrane. They have also some tendency to affect the bowels. They are essentially irritant, and are contraindicated by inflammation or oversensitiveness of the alimentary mucous membrane. They are especially indicated by loss of appetite, when such loss of appetite is the outcome of a depressed condition of the stomach, but when it is the result of gastro-inflammation they will do harm. A second class of stomachics are the so-called *aromatics*, which depend for their activity upon the presence of a volatile oil. They differ from the simple bitters in being more powerful but less permanent as local stimulants. (See page 478.) A third class of drugs contain both volatile oil and bitter principle, and unite the properties of the aromatics with those of the simple bitters. These are the so-called *aromatic bitters*.



## SIMPLE BITTERS.

## QUASSIA.

Under the name Quassia the United States Pharmacopœia recognizes the wood of the *Picrasma excelsa* (Jamaica quassia), a large tree growing in the island of Jamaica, and of the *Quassia amara* (Surinam quassia), a shrub found in Guiana and neighboring parts of South America. Each of these contains a bitter principle; these while closely allied chemically, are not regarded as identical. The precise chemical nature of these principles, known respectively as *picrasmin* and *quassin*, is not clearly understood.

## Official Preparations :

Extractum Quassiæ.....	1 to 3 grains (0.06–0.2 Gm.).
Fluidextractum Quassiæ.....	5 to 10 minims (0.3–0.6 C.c.).
Tinctura Quassiæ (20 per cent.).....	$\frac{1}{2}$ to 1 fluidrachm (2–4 C.c.).

**Physiological Action.**—Quassia can hardly be said to be poisonous to man, the largest doses producing in the adult only gastric irritation, but F. Venn has reported a case in which in a young child the injection into the rectum of a decoction representing two ounces of quassia was followed almost immediately by vomiting, stupor, relaxation, and collapse, ending in death. According to I. Hoppe, *quassin*, when given to frogs in doses of one grain, will produce weakness, convulsions, respiratory and cardiac failure, ending in death. Locally, *quassin* is a distinct irritant. In man, five milligrammes of the pure crystalline form notably increased the secretion of bile and of urine, and caused some looseness of the bowels and stimulation of the bladder; while fifteen milligrammes produced violent frontal headache, burning pains in the œsophagus and throat, nausea, vomiting, vertigo, excessive nervous restlessness, diarrhœa, and very frequent micturition, but diminished renal secretion.\*

**Therapeutics.**—Quassia is probably the most active of all the simple bitters, and may be used whenever such remedies are indicated. In cases of *seat-worms* in children, a strong infusion of quassia (two ounces to one pint) affords a most harmless and efficient injection. Its exhibition should be preceded by an enema of simple water, after a stool, so as thoroughly to wash out the rectum and allow access to every fold of the rectal mucous membrane.

## GENTIAN.

The root of *Gentiana lutea*, or the yellow gentian of the Alps. This root occurs either in pieces of various sizes and shapes, but usually several inches in length, or else in transverse slices. The texture is spongy, the odor peculiar, and the taste bitter. It contains *gentisic acid*, which was discovered by Leconte and is tasteless and physio-

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\* B. G. T., ciii. 410.

logically inert. The active principle is probably *gentiopikrin* (Kromayer), a neutral, crystalline substance, of an intensely bitter taste.

**Official Preparations:**

Extractum Gentianæ.....	2 to 4 grains (0.13-0.26 Gm.).
Fluidextractum Gentianæ.....	10 to 30 minims (0.6-2.0 C.c.).
Tinctura Gentianæ Composita (10 per cent.).....	1 to 4 fluidrachms (4-16 C.c.).

**Therapeutics.**—Gentian is one of the most efficient of the simple bitters, and may be used whenever such a remedy is indicated. The most largely used of its preparations is the compound tincture, which contains gentian, bitter orange peel, and cardamom.

**CALUMBA.**—The root of *Jateorhiza palmata*, a climbing vine of Mozambique. It occurs in the shops in transverse disk-like slices, oval or circular in outline, one or two inches in diameter, of a spongy texture, having a yellowish surface, a very bitter taste, and a slightly aromatic odor. It contains a great deal of starch, besides berberine, and, it is said, in lesser amount, *columbin*, a bitter neutral principle crystallizing in rhomboid prisms or needles. F. Roux has found that columbin given to pigeons in doses of ten centigrammes produces death, preceded by failure of the appetite, marked signs of gastro-intestinal irritation, and jaundice.

**Official Preparations:**

Fluidextractum Calumbæ.....	15 to 30 minims (1-2 C.c.).
Tinctura Calumbæ (10 per cent.).....	1 to 2 fluidrachms (4-8 C.c.).

**CHIRATA**, the herb and root of *Swertia Chirayita*, a plant growing in the northern part of India, is one of the best of the simple bitters, and is believed by some to exert a peculiar influence over the liver. Whenever a simple bitter is indicated, this drug may be employed, especially if a cholagogue action be desired.

Fluidextractum Chiratæ.....	5 to 10 minims (0.3-0.6 C.c.).
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**BERBERIS.**—The root and berries of *Berberis vulgaris* of Europe have long been used abroad as a simple laxative tonic, and the U. S. Pharmacopœia recognizes the rhizome and roots of *B. Aquifolium* and other species. These plants depend for their slight medical activity upon the presence of berberine (see *Hydrastis*) and other feeble alkaloids. They have been used in atonic *dyspepsia*, especially when with hepatic torpor; also as alteratives in constitutional *syphilis*.

Fluidextractum Berberidis.....	30 minims (2 C.c.).
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## WILD CHERRY.

Wild cherry bark is the product of *Prunus (Cerasus) serotina* or wild cherry tree, not of *Prunus Virginiana* or choke-cherry, whose name it bears. It occurs in pieces of various sizes, usually without epidermis. The color is a reddish cinnamon; the taste slightly astringent, bitter, and peculiar, resembling that of peach-leaves. It

contains tannic acid, bitter extractive, a nitrogenous, crystallizable, odorless glucoside (*amygdalin*), and an albuminous principle (*emulsin*). When amygdalin in aqueous solution is brought in contact with emulsin, it is decomposed, forming prussic and formic acids and a colorless, thin, volatile oil, which, when pure, has a peculiar, agreeable odor and a burning taste. According to Liebig and Wöhler, seventeen grains of amygdalin yield one of hydrocyanic acid: therefore, if thirty-four grains of amygdalin be mixed with sixty-six grains of an emulsion of sweet almonds, a two-per-cent. (by weight) solution of hydrocyanic acid will be formed.

#### Official Preparations:

Fluidextractum Pruni Virginianæ . . . . .  $\frac{1}{2}$  to 1 fluidrachm (2-4 C.c.).

Syrupus Pruni Virginianæ (15 per cent.) . . . 1 to 4 fluidrachms (4-15 C.c.).

Infusum Pruni Virginianæ (4 per cent.) . . . 2 to 4 fluidounces (60-100 C.c.).

**Physiological Action.**—Amygdalin is physiologically inert, as much as sixty grains having been taken without result. Fifteen grains may cause death in the rabbit, but this is owing to its being converted into prussic acid by the emulsin in the herbage in the rabbit's stomach.\*

**Therapeutics.**—In wild cherry bark properly administered there are three active ingredients,—tannic acid, bitter extractive, and prussic acid. The amount of prussic acid is too small to cause perceptible effects, so that wild cherry bark is simply a feeble astringent and tonic. It has been very largely used in *phthisis*, and has been supposed not only to act as a tonic and astringent, but also to exert a calnalmative influence on the nervous system.

**OREXIN.**—*Phenylidihydrochinazoline Hydrochlorate*, or *Orexæ Hydrochlorate*.—This complex derivative of quinoline occurs as colorless, odorless crystals, with bitter pungent taste: freely soluble in hot water. Originally brought forward by F. Penzolt as a true stomachic it has been variously reported upon by clinicians. According to the general reports, and especially to the experiments of Hofmann, it is practically nontoxic, two grains per pound weight not being sufficient to kill a rabbit, although after enormous doses free hemoglobin appears in the blood. Orexin hydrochlorate has, however, been entirely superseded by the *orexin tannate*, a yellowish, tasteless, odorless powder, insoluble in water but freely soluble in acid solutions, and consequently in the gastric juice. There seems to be little doubt but that orexin tannate is a valuable gastric stimulant in all those cases in which a simple bitter is indicated, and that it is contraindicated by gastric inflammation or hyperacidity, and by gastric ulcer. It is stated, also, to be effective against the *vomiting* following the use of opium, chloroform, and other narcotics, and also in the *vomiting of pregnancy*. It is chemically incompatible with iron salts. Dose, five to twelve grains, one to two hours before meals. Owing to the insolubility of the salt it is much better to give it in powder than in tablets.

#### AROMATICS.

The aromatic oils are essentially local irritants, causing when taken into the mouth intense burning pain, and when confined upon the skin, rubefaction, blistering, and finally, if the contact be very prolonged, more destructive changes. Internally, taken in very large

\* See Husemann (*Die Pflanzenstoffe*).



doses, they cause burning pain in the stomach, increased activity of the circulation, and a species of intoxication. In sufficiently large quantities they are irritant narcotic poisons. When administered in therapeutic doses they act almost exclusively upon the alimentary canal. As compared with that of the simple bitters, their influence is more powerful and more transient. They do not permanently increase the digestive power, but simply increase action for the time being. They are employed chiefly to increase the immediate stimulant effect of bitter tonics upon the secretory digestive glands; as *carminatives*, to stimulate the intestines to contract upon and expel flatus; to prevent the griping of purgatives; to disguise the taste of medicines, and to render nauseating drugs acceptable to the stomach; and to act as condiments and aid in the digestion of the food.

It is probable that aromatics directly after their ingestion affect more powerfully the digestive glandular apparatus than do bitter tonics, since Gottlieb has shown that such substances as mustard, which are local irritants to the stomach, cause a very marked increase in the secretion of the pancreatic fluids. Even when the gland had almost ceased its function, oil of mustard introduced into the stomach or duodenum caused active secretion in the pancreas. Quassia, taken as a type of the bitters, had no effect on the pancreatic activity.

Injected into the circulation, most volatile oils lower the blood-pressure by depressing the heart's action, and even in comparatively small doses may cause immediate diastolic arrest. In this respect oil of cloves is one of the most powerful. Their cardiac action is undoubtedly direct and upon the heart itself: other muscular structures would seem to be similarly affected, as H. Kobert has found that the oil of mace directly lowers muscular excitability.\*

When in concentrated form almost all of the volatile oils are direct paralyzants to nerve-tissues, and seem to act especially upon the sensory nerve-endings; hence most of them are local anesthetics, and some are used for this purpose in practical medicine. Most of them also possess antiseptic properties.

Some of the tonic drugs containing a volatile oil also have in them a bitter principle which modifies their action. Such drugs may be known as *aromatic bitters*; as bitters they are less powerful than such drugs as quassia, and are especially indicated when the stomach is delicate and easily nauseated.

*Inflammation of the stomach or bowels* is the chief contraindication to the use of aromatics. Unlike the simple bitters, they are often very useful in *diarrhæa* of nervous irritability or of relaxation, when no decided inflammation exists.

\* Masoin and Bruylant have studied to some extent the physiological action of the oils of *lavender*, *rosemary*, *myrrorani*, and *aspic* (*Lavandula spica* L.) (Bull. Acad. Roy. Méd. de Bruxelles, 1879, 558; see also *Schmidt's Jahrb.*, clxxx, 123, and Cadeac and Meunier, *Compt.-Rend. Soc. Biolog.*, 1889, and *Lyon Méd.*, 1889). In frogs they caused generally paralysis, with loss of reflex activity; the muscles being intact, and the sensory nervous apparatus being affected before the motor. Upon the higher animals a similar effect was produced, except that oil of rosemary caused epileptiform convulsions. *Oil of Peppermint* (*M. piperita*) has been studied by S. D. Markuson (*Inaug. Diss.*, Halle, 1877; *Schmidt's Jahrb.*, clxxx, 122), who finds that while very small doses increase, larger ones decrease the blood-pressure and lower the bodily temperature. Most of the volatile oils have germicidal properties, and the oil of peppermint has been highly praised as a practical dressing for burns, wounds, etc. (See *The Medical Reporter of India*, vi.)

**Official Preparations :**

The following are the official preparations whose activity is chiefly owing to a volatile oil.

Oleum Anisi.....	3 to 5 minims (0.2-0.3 C.c.).
Aqua Anisi.....	Vehicle.
Spiritus Anisi (10 per cent.).....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Oleum Aurantii Corticis.....	3 to 5 minims (0.2-0.3 C.c.)
Spiritus Aurantii Compositus (Oils of Orange, Lemon, Coriander and Anise).	
Syrupus Aurantii.....	Vehicle.
Tinctura Aurantii Dulcis.....	Vehicle.
Elixir Aromaticum (1.2 per cent. of Com- pound Spirit of Orange).....	Vehicle.
Elixir Adjuvans (Aromatic Elixir and Fluid- extract of Licorice).....	Vehicle.
Fluidextractum Aurantii Amari.....	15 to 30 minims (1-2 C.c.).
Tinctura Cardamomi.....	1 to 2 fluidrachms (4-8 C.c.).
Tinctura Cardamomi Composita.....	Vehicle.
Oleum Caryophylli.....	3 to 5 minims (0.2-0.3 C.c.).
Eugenol—Synthetic Oil of Cloves.....	3 to 5 minims (0.2-0.3 C.c.).
Oleum Cinnamomi.....	1 to 3 minims (0.06-0.2 C.c.).
Cinnaldehydum.....	1 to 3 minims (0.06-0.2 C.c.).
Spiritus Cinnamomi (10 per cent.).....	15 to 30 minims (1-2 C.c.).
Aqua Cinnamomi.....	Vehicle.
Tinctura Cinnamomi.....	1 to 2 fluidrachms (4-8 C.c.).
Oleum Fœniculi.....	3 to 5 minims (0.2-0.3 C.c.).
Aqua Fœniculi.....	Vehicle.
Oleum Gaultheriæ.....	5 to 30 minims (0.3-2.0 C.c.).
Oleum Betulæ.....	5 to 30 minims (0.3-2.0 C.c.).
Spiritus Gaultheriæ (5 per cent.).....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Oleum Lavandulæ Florum.....	3 to 5 minims (0.2-0.3 C.c.).
Spiritus Lavandulæ (5 per cent.).....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Tinctura Lavandulæ Composita.....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Oleum Limonis.....	3 to 5 minims (0.2-0.3 C.c.).
Limonis Succus.....	$\frac{1}{2}$ to 1 fluidounce (15-30 C.c.).
Tinctura Limonis Corticis.....	Vehicle.
Oleum Menthæ Piperitæ.....	3 to 10 minims (0.2-0.6 C.c.).
Menthol.....	1 to 2 grains (0.06-0.12 Gm.).
Spiritus Menthæ Piperitæ (10 per cent.).....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Aqua Menthæ Piperitæ.....	Vehicle.
Oleum Menthæ Viridis.....	3 to 5 minims (0.2-0.3 C.c.).
Spiritus Menthæ Viridis (10 per cent.).....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Aqua Menthæ Viridis.....	Vehicle.
Oleum Myristicæ.....	5 to 10 minims (0.3-0.6 C.c.).
Oleum Pimentæ.....	3 to 5 minims (0.2-0.3 C.c.).
Oleum Rosmarini.....	3 to 5 minims (0.2-0.3 C.c.).
Oleum Sassafras.....	3 to 5 minims (0.2-0.3 C.c.).
Pulvis Aromaticus (Contains Cinnamon, Ginger, Cardamom and Nutmeg).....	5 to 15 grains (0.3-1.0 Gm.).
Fluidextractum Aromaticum (100 per cent. of Aromatic Powder).....	5 to 15 minims (0.3-1.0 C.c.).

CINNAMON.—The U. S. Pharmacopœia recognizes Saigon Cinnamon, the bark of an undetermined species of the genus *Cinnamomum*, which comes from Cochin China; it also recognizes *Ceylon Cinnamon*, the bark of the *Cinnamomum zeylanicum*. Much of the cinnamon of the markets comes from China and is known as *Cassia Bark*, or *Chinese Cinnamon*. Of these barks the Ceylon is considered the finest and the Cassia the poorest in quality. They all contain tannic acid and a yellowish volatile oil which, on account of its great fragrance and very pleasant taste, is largely used as an adjuvant or to disguise the flavor of less agreeable drugs. Oil of cinnamon contains seventy-five to ninety per cent., by volume, of *cinnamic aldehyde*—CINNALDEHYDUM, U. S.—which may also be prepared synthetically. It is a colorless, aromatic liquid, having the same medical properties as has the oil itself.

CLOVES are the unexpanded flowers of *Eugenia aromatica*, a tree native to the Molucca Islands. This source, however, is practically exhausted and the present supply comes from cultivated trees in the West Indies, the islands of the Indian Ocean and other tropical regions. They owe their properties to an exceedingly pungent volatile oil, yellowish when fresh, but becoming darker with age. The oil of cloves should contain not less than eighty per cent. of *eugenol*. This latter is an unsaturated phenol corresponding in its physical properties to the oil of cloves. Oil of cloves, besides being used as a carminative and an aromatic, is often employed to benumb sensitive dentine, or even exposed pulp, in *caries* of the teeth. Dropped on a piece of cotton and placed in the cavity, it is much used to relieve *toothache*.

Oil of cloves is chiefly composed of an unsaturated phenol, *EUGENOL*, U. S., which is a colorless or yellowish thin liquid, having the odor and taste of cloves, and becoming on exposure to the air dark and thick. It may be used for the same purposes as is the oil of cloves. *Clove tea*, two drachms to the pint, an infusion made with boiling water, is often used domestically in doses of a wineglassful or more for acute *menstrual suppression* and as a sudorific.

NUTMEG (*Myristica*) is the kernel of the ripe seed of *Myristica fragrans*, a tree growing in the Molucca Islands. The nutmeg contains both a fixed and a volatile oil. *Mace* (U. S. P. 1890) is the arillus or outer imperfect supernumerary coating of the seed. Both mace and nutmeg depend for their activity upon the volatile oil of nutmeg. This, when injected intravenously into the lower animals, causes loss of coördination, tremors, profound coma, abolition of all reflexes, and finally death from respiratory paralysis, its influence upon the circulation being comparatively feeble.\* In man, one or two nutmegs will usually suffice to produce a dreamy, half-unconscious intoxication, and severe or even fatal poisoning has been caused by larger

\* Experiments of H. C. Wood; also Cadeac and Meunier (*Journ. Méd. Vét.*, Lyons, 1890).



quantities. The symptoms of poisoning have been dizziness, stupor deepening into coma, muscular relaxation, dilated pupils, slow pulse and respiration, and suppression of urine, ending in death from respiratory paralysis.\* In animals fatally poisoned fatty degeneration has been found (Wallace.)

PIMENTA or *Allspice* is the unripe berries of *Pimenta officinalis*, a tree, native in the West Indies.

CARDAMOM is the fruit of *Elettaria repens*, which grows in the East Indies. It consists of tough, seemingly fibrous, generally more or less triangular dry and tasteless capsules, containing a number of small, hard, very aromatic seeds. The colorless, highly aromatic, volatile oil is not official. Cardamom is a very grateful aromatic, much less stimulating and heating than most of the other drugs of its class. The compound tincture is a very elegant addition to, or vehicle for, tonic medicines.

GINGER (*Zingiber*) is the dried rhizome or root-stock of *Zingiber officinale*, growing in the East and West Indies. *Green Ginger* is the fresh rhizome. *Black Ginger* is the root-stock dried with the epidermis on; *White* or *Jamaica Ginger* is the same, deprived of its epidermis. The fresher ginger is the greater is its power, and by time and exposure it becomes completely inert. Its active principles are a soft, acrid, aromatic resin, and a yellow, volatile oil. Ginger is much used in domestic medicine as a stimulant carminative in *colic*; given in hot water, it is also used as a sudorific and stimulant in the pain due to *suddenly suppressed menstruation*. It is often added with advantage to other remedies in *dyspepsia*. The syrup is used only as a cordial drink or vehicle.

#### Official Preparations :

Oleoresina Zingiberis.....	$\frac{1}{2}$ to 2 minims (0.03–0.12 C.c.).
Fluidextractum Zingiberis.....	5 to 10 minims (0.3–0.6 C.c.).
Tinctura Zingiberis (20 per cent.)—Essence of Ginger.....	$\frac{1}{2}$ to 1 fluidrachm (2–4 C.c.).

PEPPER.—*Black Pepper* is the unripe fruit of *Piper nigrum*, a woody vine-like plant growing in the East Indies. *White Pepper* is the ripe berries stripped of their skin and dried. It is much less pungent than the black pepper. The active principles of black pepper are a soft, acrid resin, a pungent, fiery, volatile oil, and piperine.

In 1819 Oersted discovered *Piperine*, which crystallizes in colorless, glistening, four-sided, truncated prisms, of a neutral reaction, but capable of combining with acids to form salts. When pure it is tasteless; but very commonly it has a burning taste, due to the presence of some of the volatile oil of pepper. The possession of very active antiperiodic properties has been asserted for piperine, and it

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\* Fatal case, *N. Y. Med. Record*, Nov. 1886. Collection of Cases, George B. Wallace, *C. M. R. V.*, 362.

was for a time employed in *intermittent fever*; but it has fallen into complete disuse. Pepper is very largely used as a condiment; but, as its taste is more hot than aromatic, it is rarely given internally in medicine except as an addition to simple bitters or to antiperiodics, generally in the form of the oleoresin. In atonic *dyspepsia* the latter preparation is an excellent adjuvant to tonic pills. Schiffer is said (Fließ) to have used piperine successfully in a case of *vaginismus*, by injecting three-tenths of a grain (0.018 Gm.) hypodermically near the vaginal entrance. In using piperine by hypodermic injections it is of the utmost importance to see that it is free from the oil of pepper.

#### Official Preparations:

Piper.....	5 to 10 grains (0.3–0.6 Gm.).
Oleoresina Piperis.....	$\frac{1}{2}$ to 1 grain (0.03–0.06 Gm.).
Piperina.....	3 to 5 grains (0.2–0.3 Gm.).

**CAPSICUM.**—The U. S. Pharmacopœia now recognizes only the small,—less than an inch long,—very fiery fruit of *Capsicum fastigiatum*, the *African Pepper*, or *Chillies*. The large, bright red, conical or ovate, comparatively mild peppers of the market are from *C. annum*; they are sometimes known as *West India peppers*. *Capsicum* contains as its active principle an exceedingly acrid oleoresin.\*

*Capsicum* is a very powerful local irritant, its oleoresin when applied to the skin producing in a very few minutes intense pain and redness, and finally destroying the cuticle. In the alimentary canal it acts in a similar manner: thus, moderate doses produce merely a pleasant feeling of warmth in the stomach, while overdoses may cause gastro-intestinal inflammation, with severe pain, as well as vomiting and purging, followed after a time by strangury and other evidences of genito-urinary irritation. The chief use of *Cayenne Pepper* is as a condiment; yet it is often added with advantage to tonic pills to increase their immediate action on the stomach. When there is habitual feeble digestion, with flatulence, its free use on food may do good. In *adynamic diseases*, especially as occurring among *drunkards*, *capsicum* is often very useful by stimulating the stomach up to the point of digesting food. *Locally*, either as the diluted tincture in a gargle or applied in powder or tincture by means of a swab, it is useful in *severe tonsillitis*, especially in that accompanying scarlet fever.

#### Official Preparations:

Capsicum.....	1 to 3 grains (0.06–0.2 Gm.).
Oleoresina Capsici.....	$\frac{1}{2}$ to $\frac{1}{2}$ minim (0.01–0.03 C.c.).
Fluidextractum Capsici.....	1 to 3 minims (0.06–0.2 C.c.).

### AROMATIC BITTERS

**ANTHEMIS.**—**CHAMOMILE.**—*Roman* or *true Chamomile*, the dried flower heads of *Anthemis nobilis*, a composite of Europe, contains a bluish or sometimes greenish volatile oil, a bitter principle, and a

\* The name of *Capsicin* has been applied by different observers to the oil, to the resin, and to their combination, but has no definite meaning.

small amount of tannin. The infusion (one ounce to a pint) is a mild stomachic in doses of one to two wineglassfuls. *MATRICARIA*, or *German Chamomile*, the dried flower heads of *Matricaria Chamomilla*, is much less agreeable and effective.

*SERPENTARIA*.—The dried rhizome and roots of *Aristolochia Serpentaria* and of *A. reticulata*, small herbal plants of the United States, contain a volatile oil, a yellowish-green resin, and a bitter principle. It is an elegant stimulant tonic, especially useful as an adjuvant to more powerful bitters.

#### Official Preparations :

Tinctura Serpentariæ (20 per cent.).....1 to 2 fluidrachms 4-7 C.c.).  
 Fluidextractum Serpentariæ .....20 minims (1.2 C.c.).

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## FAMILY II.—EMETICS.

EMETICS are those drugs which are employed in the practice of medicine for the purpose of producing emesis, or vomiting.

Vomiting occurs under two provocations, or in two manners. Thus, a mental impression, or a disordered state of the blood, may influence the nerve-centres directly, and emesis, spoken of as *centric*,

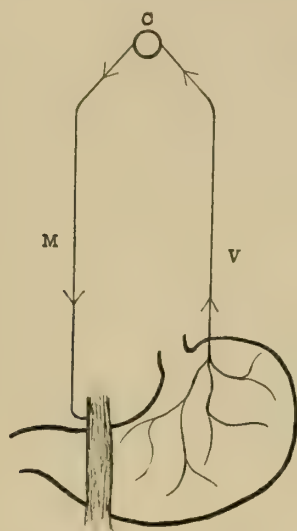


FIG. 17.—DIAGRAM TO SHOW THE MODE OF ACTION OF EMETICS.

C.—Vomiting centre. V.—Pneumogastric nerve conveying impulses from the stomach to the centre. M.—Motor nerve running to abdominal muscle. (For simplicity the other efferent nerves concerned in the act of vomiting are not represented. Some drugs as zinc sulphate and mustard irritate the sensory nerves in the stomach and cause vomiting reflexly. Apomorphine acts directly on the vomiting centre (C). Ipecac and antimony probably act in both ways.

results; or a peripheral irritation in the stomach itself, or in some other organ, as in the kidneys, may induce vomiting precisely similar in the method of its production to the more ordinary reflex movements; such vomiting is called *reflex* or *excentric*.

Emetics produce their results in both of these methods. Thus, tartar emetic has been believed to affect the centres directly, so as to cause centric vomiting, while copper sulphate has been believed to irritate the mucous membranes of the stomach, so as to produce reflex vomiting. Much doubt, however, has been thrown upon the old views, and it is probable that most emetics have a double influence. Thus, the purging of arsenic or of tartar emetic is almost certainly

connected with its elimination, and is probably due to a direct action of the circulating poison upon the intestinal mucous epithelium, gland-cells, and peripheral nerves. It seems *a priori* almost a necessity that the vomiting caused by these poisons is produced in the same way as is the purging. D'Ornellas has found that when emetine is injected into the veins of animals the vomiting occurs simultaneously with the elimination of the alkaloid from the gastric mucous membrane, and asserts that Kleimann and Simonowitsch have determined the same thing with antimony. Further, antimony seems to cause vomiting partly by acting upon the centres, partly by irritating the peripheral nerve. Irritant emetics are more prompt than those which chiefly affect the nerve-centres; they always cause less nausea and general systemic disturbance than do the centric emetics.

Another evident practical fact is, that while centric emetics will act in whatever way they are introduced into the system, the mechanical emetics must be exhibited by the stomach. Thus, apomorphine may be given by hypodermic injection, but mustard must be taken by the mouth. Nevertheless, it is probable that most of the so-called "irritant emetics" act in part by being absorbed, since A. Sacher has found that even zinc sulphate will, when injected in proper dose into the blood, produce vomiting, and Brunton and West have demonstrated that a peptone of copper injected into a vein causes violent vomiting.

A very curious property of emetics has been pointed out by E. Harnack, who, as the result of an elaborate investigation, affirms as a law that all specific emetic substances destroy, even when in relatively small dose, the excitability of striated muscular fibre. Harnack seems to establish the general truth of this; but that it is universal law is scarcely probable, and the connection between the two properties is very obscure. According to H. Kobert, antimony has an effect on muscle-fibre only when the contact is prolonged.

In regard to the phenomena of vomiting, there are a few points to which it is necessary here to call attention. First of these is the fact that *nausea* always produces, or is accompanied by, muscular relaxation. Vomiting may take place, as from mustard, without much relaxation; but when it is accompanied by much nausea the whole system is, as it were, unbent, the skin relaxed and bedewed with perspiration, the pulse soft and feeble, the muscular system limp and incapable of exertion, and the mental acts almost suspended. During violent vomiting the blood is driven to the head, so that the whole exterior of the cranium, and probably the interior also, becomes very much congested. The abdominal circulation is greatly affected, and the blood is, as it were, squeezed out of the portal vein and its tributaries. The matters rejected consist of the contents of the stomach, and, in repeated vomiting, also those of the duodenum. The secretion from the gastric mucous membrane is very much enhanced, and without doubt is more or less modified. Bile in ejecta is to be recognized by the green color and the bitter taste, or more infallibly by testing with the proper reagents.

The indications for the use of emetics are as follows:

1. *To unload the Stomach.*—For this purpose they are employed in poisoning, or when the stomach is oppressed by indigestible substances or by its own acrid, perverted secretions. The symptoms induced by irritating materials in the stomach are various, and sometimes it requires a good deal of tact or experience to recognize their cause. Among them may be mentioned a feeling of weight or load in the stomach, gastric distress, or severe cramp or spasmodic pains, with or without some nausea and retching. In other cases no local manifestations of trouble may be present. Thus, *convulsions* in children are very frequently the result of gastric irritation, and are at once relieved by emptying the stomach. In adults, *apoplectic coma* may offer a similar history. Occasionally *urticaria*, or hives, and not rarely severe *headache*, have a similar origin, and require a similar treatment.

2. *To affect the Abdominal Viscera and Circulation.*—In *congestions* of the *portal* circulation, especially such as follow a debauch, and in the condition of digestive derangement known as *biliousness*, emetics are often of service. In *catarrhal jaundice* they may effect much good by causing dislodgement of the mucus plugging the ducts. They have been employed in cases of *biliary calculi*; but the chances of forcing out the calculus by external violence are probably no greater than those of lethal rupture of the gall-bladder.

3. *To dislodge Substances from the Respiratory Passages.*—For this purpose emetics are sometimes used when foreign bodies have found entrance into the larynx; but it is chiefly in *membranous croup* that the present indication is met with. The emetics chosen for this purpose should be such as act with violence without producing much nausea or systemic disturbance: the mechanical emetics are therefore the best.

4. *To produce Muscular Relaxation.*—The introduction of anesthesia has rendered the use of emetics to meet this application almost obsolete. Occasionally, however, in *asthmatic* or other *spasmodic affections* of the respiratory organs, emetics are still employed. For this purpose the drugs causing much nausea are preferred. In adults, lobelia is the best; in children, ipecacuanha. Nauseating rather than emetic doses should be employed.

*Contraindications.*—The chief contraindications to the use of emetics are the existence of congestion of the brain and of gastric inflammation. Advanced pregnancy, and hernia, while they do not positively contraindicate the use of emetics, should cause great caution to be practised in their employment.

*Administration.*—Emetics should, as a general rule, be given in a full dose, so as to avoid unnecessary repetition, and should be administered dissolved in water or in syrup. Their action should be assisted by frequent and copious draughts of tepid water, which also have the advantage of rendering the vomiting less painful. When for any reason protracted nausea is desired, the doses should be small and repeated at short intervals.



*Hyperemesis* may advantageously be divided into two varieties: first, such as is due to overdoses of depressing centric emetics; second, such as arises from irritation of the stomach, as by mechanical emetics. The treatment of the first of these consists in the enforcement of absolute quiet in the horizontal position, the free use of opium enemata, the application of counter-irritants to the epigastrium, and the use of alcoholic stimulants. The latter should be given in hot water, and should not be too much diluted. We have seen raw brandy arrest at once the most alarming centric emesis after the failure of other methods. Cocaine, creosote, chloroform, or chloroform and volatile oils are sometimes of value in this form of hyperemesis. When excessive vomiting is due to some irritant substance, the stomach should be thoroughly washed out by large draughts of warm mucilage, opium given by the rectum, a mustard plaster or blister, or, often better still, leeches applied to the epigastrium, and no medicine at all be taken into the inflamed viscus. The swallowing of small pieces of ice is sometimes of service. If these remedies fail, the treatment of this form of hyperemesis soon resolves itself into that of gastritis.

## CENTRIC EMETICS

### IPECACUANHA.

The U. S. Pharmacopœia recognizes the *Cephaëlis Ipecacuanha*, growing in Brazil, and the *C. acuminata*, growing in Colombia, small shrubs whose roots respectively constitute the Rio, Brazilian, or Para ipecacuanha, and the Carthagena ipecacuanha. There is at present no sufficient reason for believing that these plants are specifically distinct. (See U. S. Dispensatory, 19th edition.) The true ipecacuanha plant has been cultivated with success in the Straits Settlements, producing the so-called Johore ipecacuanha. The South American drug comes from wild plants exclusively.

These roots are from one-eighth to one-fourth inch in diameter and four to eight inches long, brown or grayish in color, variously bent and contorted and marked on the surface with numerous prominent rings. The root itself has but very little odor but when powdered has a dusty, peculiar smell and in some persons excites sneezing. The taste is bitter, acrid and nauseous. They depend for their activity upon the presence of two alkaloids, *emetine* and *cephaëline*. There is a third alkaloid *psychotrine*, which is, however, almost inert.

The ipecacuanha roots differ largely in the total percentage of the alkaloidal contents, hence the requirement of the U. S. Pharmacopœia that they should contain at least 1.7 per cent. of aggregate alkaloids. It has been believed by various authorities that the Rio and Carthagena ipecacuanhas—because in the former *emetine*, in the latter *cephaëline*, predominates—are not interchangeable; but the reports of the large drug firms both in Europe and in this country indicate that the individual roots of either vary as much in the

proportionate percentage of emetine and cephaeline as do Rio and Carthagena ipecacuanha, and that, therefore, these two ipecacuanhas may be considered as therapeutically identical. Practical differences in their action have not been made out by clinicians; and the belief of some experimentalists that when an emetic effect is desired Carthagena is best, and when an expectorant effect is wished Rio ipecac should be used, is not well founded.\* *Ipecacuanhic acid*, with which the alkaloids are combined, according to Kimura, is practically inert, although when brought in contact with the red blood-corpuscles outside of the body it dissolves out the hemoglobin.

#### Official Preparations :

Ipecacuanha.....	Emetic Dose 30 grains (2 Gm.).
Pulvis Ipecacuanhæ et Opii— Dover's Powder—(10 per cent.).....	3 to 10 grains (0.2–0.6 Gm.).
Fluidextractum Ipecacuanhæ. {	Expectorant 1 to 5 minims (0.06–0.30 C.c.).
	Emetic 30 minims (2 C.c.).
Tinctura Ipecacuanhæ et Opii (10 per cent.).....	3 to 10 minims (0.2–0.6 C.c.).
Syrupus Ipecacuanhæ (7 per cent.).....	5 to 20 minims (0.3–1.2 C.c.).
Vinum Ipecacuanhæ (10 per cent.)	Emetic Dose..... $\frac{1}{2}$ to 1 fluidounce (15–30 C.c.).

*Local Action.—Absorption and Elimination.*—Locally applied, ipecacuanha is a decided irritant, manifesting its action not only upon mucous membranes and upon denuded surfaces, but also causing, when applied by inunction, an eruption of small, discrete pustules, with a rather large areola, followed, it may be, by large pustulation and even severe ulceration. Both pure emetine and cephaeline were found by Lowin to be very irritant, and especially so to mucous membranes. Ipecacuanha rapidly yields its active principles to absorption. They are probably eliminated by the stomach, intestines and kidneys, but concerning this we have no definite knowledge†.

*Physiological Action.*—When given in small repeated doses to man, ipecacuanha produces malaise, with nausea, and perhaps an increase of the secretions of the salivary glands and of the mucous membranes of the bronchial tubes and of the stomach. In large amounts it causes vomiting, accompanied by only a moderate amount of nausea, but by a decided increase of the secretions mentioned above. The vomiting, even when very large amounts are taken into the stomach, is not likely to be severe, nor the prostration marked.

The general physiological action of ipecacuanha is extremely feeble, although its alkaloids are certainly very active substances. The difference is probably due to the fact that ipecacuanha is

\* According to the experiments of Carl Lowin emetine is only a feeble emetic, while cephaeline is a very powerful emetic. On the other hand, cephaeline does not act upon the lungs at all, so that the emetic influence of ipecacuanha is dependent upon the presence of cephaeline,—its expectorant influence upon the presence of emetine.

† According to Maurel (*Merck's Bericht*, 1901) the lethal dose of emetine on the pigeon and rabbit is 0.15 gramme per kilo. Maurel also states that emetine acts upon the rabbit as a local anesthetic.

rejected from the stomach before it can be taken in sufficient dose to yield poisonous amounts of its alkaloids to absorption.

According to D'Ornellas, toxic doses of commercial emetine cause in the frog diminished sensibility, muscular feebleness deepening into abolition of voluntary movement, with at first increased and afterwards diminished activity, and finally death from failure of respiration; in the mammal, similar symptoms, with the addition usually of severe vomiting.

*Nervous System.—Respiration.—Circulation.*—According to D'Ornellas and Pecholier, commercial emetine exerts no influence upon the cerebrum, but acts powerfully upon the motor side of the spinal cord,—in the frog killed with it both nerve and muscle retaining their susceptibility to feeble galvanic currents (D'Ornellas, Pecholier and Foulkrod). It causes death by respiratory paralysis, which is probably of centric origin.

The action of commercial emetine upon the circulation appears to be feeble, since Dyce Duckworth has shown that the fall of arterial pressure which the crude alkaloid produces does not occur until late in the poisoning. The fall is chiefly of cardiac origin. Lowin has found that pure emetine and pure cephaeline diminish the rate and strength of the contraction of the isolated frog's heart, cephaeline being the feeble of the two alkaloids. Psychotriné had no distinct effect. Lowin also found that both cephaeline and emetine paralyze the heart in warm-blooded animals.

*Pulmonic and Digestive Organs.*—As emetine injected hypodermically causes vomiting, ipecacuanha must be looked upon as a centric emetic; but the observation of D'Ornellas, that the emetine produces vomiting much more slowly when thrown into the veins than when given by the stomach, indicates that the local irritant action of the drug is a factor in the production of emesis.

The great influence of the drug upon the abdominal viscera is further shown by the fact, attested by Pecholier, Dyce Duckworth, and D'Ornellas, that in emetine-poisoning, although there is a distinct fall of temperature in the mouth and on the surface of the body, in the intestines the temperature either remains stationary or, more commonly, rises. Again, the changes found after death from emetine are almost exclusively in the lungs and digestive organs.

Pecholier, in his earlier experiments, found great paleness of the lungs, with intense hyperemia of the stomach and the upper half of the intestines, but in some of his later experiments the lungs were profoundly influenced. Dyce Duckworth especially noted intense hyperemia of the lungs, which were in some places emphysematous, but in other portions collapsed and even affected with true consolidation. The lesions were much less marked in the intestines than in the lungs, which resembled very closely those taken from the bodies of animals killed by section of the vagi. The pulmonic lesions were found to be most intense in the rabbit; the intestinal, in the dog, cat, and guinea-pig. Magendie first observed, years ago, the pulmonic lesions of emetine-poisoning, and D'Ornellas has likewise recorded them, but has also seen cases in which ischemia of the pulmonary tissue was found after death.

It is evident that the commercial alkaloids of ipecacuanha have a special influence upon the intestines and the lungs, but it has been a mystery why this influence should vary so in power, especially in



regard to the lungs. Carl Lowin finds that the chemically pure alkaloid produces almost equal influence on the gastro-intestinal mucous membranes; but that, while cephaeline acts violently upon the lungs, after death from pure emetine no pulmonic changes are to be found. It would seem, therefore, that the different results obtained by earlier observers have depended upon the alkaloids they have used being really varying mixtures of the two alkaloids.

**Therapeutics.**—Whenever it is desired to unload the stomach or to act by emesis upon disease, without inducing much prostration, ipecacuanha is the best of the emetics. In *narcotic poisoning* it is less certain than the “mineral emetics,” but, as it is less actively irritant to the stomach, it can be given more freely than they can, and is constantly used as an adjuvant to them. It is especially useful in the diseases of children, never causing the serious depression which tartar emetic is so liable to produce. When, however, very violent emesis is desired, as in *membranous croup*, other emetics, such as zinc sulphate, are to be preferred on account of the greater force of their action.

In *sick stomach* of nervous origin, such as occurs in *pregnancy*, minute doses of ipecacuanha have so often met with success that there can be no doubt of their value. One drop of the wine in a teaspoonful of water should be given every fifteen minutes. The use of ipecacuanha as an expectorant will be spoken of under that heading.

One of the most important uses of ipecacuanha is in *acute dysentery*, all forms of which have been treated with it with asserted advantage. Its beneficial action is most obvious in *bilious dysentery* and in *malignant dysentery*, as is indicated by the fact that its use is most common in tropical climates. In *sthenic inflammatory dysentery* it seems to be less available, although even in this it has been strongly advocated. In a valuable clinical paper, A. A. Woodhull brings forward strong evidence of the value of the remedy not only in dysentery, but also in *choleric diarrhæas*. It has likewise been used with great success in *hepatic torpor* and other forms of abdominal glandular derangement.

It probably influences not only the intestinal glands, but also the liver, since Pecholier affirms that in animals killed by it no hepatic glucose can be found. Moreover, great advantage from its use may often be obtained in the condition known as *biliousness*. In *bilious dysentery* it will often produce large tarry discharges; a change in the color of the stools sometimes follows its use in *catarrhal jaundice*. The mechanical effect of the vomiting induced by it in these cases, however, must not be lost sight of; yet it does not seem to us sufficient to account for the results, especially as some observers state that the effects noted are produced even when little or no vomiting occurs. It has been proved by D'Ornellas and Pecholier that when emetine is introduced into the circulation or into the cellular tissue it escapes with the secretions of the stomach and bowels; so that the changes which are provoked in these organs are evidently connected with the elimination of the drug.

In 1890 Surgeon-Major Harris used in dysentery the ipecacuanha root, deprived of its emetine, with alleged excellent results. His paper has given rise to considerable discussion, and Surgeon-Captain Walsh, as the result of his experiments, came to the contrary conclusion that the value of ipecacuanha in dysentery

depends upon its emetine, and devised a method of giving emetine in combination with biniodide of mercury, affirming that in this combination the drug does not produce vomiting. Other clinicians, however, have confirmed the statements of Surgeon-Major Harris. When the ipecacuanha root has been de-emetinized it fails to produce vomiting, or causes only very slight vomiting; and according to the clinical studies of Kanthack and Caddy, it has all the curative effects of ipecacuanha in *dysentery*, and does not cause depression. The freedom from alkaloid of this so-called de-emetinized ipecacuanha seems to us very doubtful.\*

As a *hemostatic*, ipecacuanha has been recommended by Trousseau, and Pecholier asserts that in *hemoptysis* it is a specific.† It has been given with asserted advantage in *flooding* after child-birth, and Carrigen asserts that it possesses oxytocic powers.

**Administration.**—As an emetic, ipecacuanha is generally administered in powder, thirty grains (2 Gm.) being given every fifteen or twenty minutes until the desired effect is produced. For a child a year old the emetic dose is five grains (0.3 Gm.). Its action should be aided and hastened by large draughts of lukewarm water. As a nauseant the dose is from two to five grains (0.13–0.3 Gm.). In dysentery it is generally best to begin with a full emetic dose, or with ten grains (0.6 Gm.) repeated every half-hour until emesis is produced. Two or three hours after vomiting, fifteen drops of laudanum should be exhibited, followed in twenty minutes by five to ten grains (0.3–0.6 Gm.) of ipecacuanha in *pill form*; this should be repeated every two or three hours, the amount of the opium being lessened, and that of the ipecacuanha increased, according to circumstances. The object is to have as much of the ipecacuanha retained as possible. Another plan is to give larger doses (twenty grains), repeated every two, four, or six hours, mustard being applied to the epigastrium and opium exhibited as before; and it is said that after two or three doses tolerance is established and the drug retained. In India, enemata of ipecacuanha are often employed, either as a substitute for or an adjuvant to its use by the mouth. This treatment has recently been imitated by Chouppe and others, and in our own practice found to be satisfactory. It undoubtedly often succeeds in *dysentery* and *choleric form* and *chronic diarrhæas*, and the gastric symptoms are almost always avoided. In chronic cases the repetition of the enemata sometimes produces so much local irritation as to forbid their continuance. We have been accustomed to give a scruple of the powder with starch and laudanum, repeated every four hours. A decoction of the drug is to be preferred, as probably causing less local irritation and being more thoroughly absorbed. To an adult, Chouppe gives daily two injections of a decoction, each lavement representing two and a half drachms of the drug.

As a counter-irritant, ipecacuanha is rarely used in this country; but in England a liniment is employed composed of four parts of the powder to fourteen parts of olive oil.

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\* See especially A. A. Woodhull (*Atlanta Med. and Surg. Journ.*, 1875).

† Consult *Pacific Med. and Surg. Journ.*, 1876.

*Emetine* has been used in doses of from one-twelfth to one-sixth of a grain (0.005-0.01 Gm.), but it is very harsh and without advantage in its action.

### APOMORPHINE HYDROCHLORIDE.

Apomorphine, which was discovered by Matthieson and Wright, is made by dehydration of morphine, usually through the action of strong hydrochloric acid. It occurs as a snow-white powder, permanent when dry, but in solution or when exposed to moisture, becoming green and finally almost black. There has been considerable discussion as to the properties of this green product; it seems, however, not to be poisonous but to lose the characteristic activity of apomorphine.

**Physiological Action.**—*Local Action.*—The soluble salts of apomorphine, when pure, are not irritant, and when used hypodermically should not cause pain. They are absorbed with great rapidity. Concerning their elimination we have no definite knowledge.

In frogs, one to five milligrammes of apomorphine cause restlessness, followed by an increasing sluggishness and muscular weakness that may end in real or apparent death. In some instances there are violent convulsions, both clonic and tonic in character.\* Sometimes recovery occurs after both respiration and cardiac action have apparently ceased.

In dogs, one to two milligrammes cause vomiting, without any other decided symptoms; after slightly larger amounts, the vomiting is severe, and accompanied by free salivation and muscular tremblings. After very large doses, vomiting does not occur, but a condition of intense restlessness, the animal jumping, running, howling, and champing constantly. The slightest noise or alarm throws the animal into violent excitement and terror; with pupils dilated and ears drawn stiffly back, he endeavors to get out of the apartment, and even to climb the wall. After still larger amounts (four or five grains), to this excitement is soon added failing muscular strength, and the hind legs are dragged behind the animal in his movements. The respiration is exceedingly hurried, and convulsions are suddenly developed. The paresis and convulsions increase, so that the animal lies upon his back, kicking wildly into the air, and finally dies asphyxiated. Rabbits cannot vomit, but the general symptoms produced by the alkaloid in them and in cats are exactly parallel with those just described as occurring in the dog. Very small doses (ten milligrammes, Harnack) suffice to kill the rabbit. On chickens and pigeons, according to C. David, it acts very much as it does upon dogs; the stage of excitement is very marked. After death no distinct lesions are to be found, unless, as Quehl believes, there is habitually an excessive hyperemia of the pons Varolii.

To the therapist the chief interest in apomorphine is in connection with its power of producing vomiting; but before taking this up we shall briefly review what is known in regard to its general actions.

**Nervous and Muscular Systems.**—The action of apomorphine upon the cerebrum seems to be that of a primary stimulant delirifacient and final paralyzant. The cause of the convulsions at present cannot be considered as determined. According to Reichert's experiments,

\* G. Valentin (*Arch. f. Exper. Path. u. Pharm.*, xi, 399).



both the sensory and motor nerves are first stimulated and afterwards paralyzed.\* In opposition to the experiments of Quehl, Harnack found that apomorphine directly affects the voluntary muscles, and as his experiments have been confirmed by Reichert, there can be no doubt that apomorphine is a muscle-poison.

*Circulation.*—The reports upon the action of this drug on the circulation are somewhat discordant. It appears to be proved that the therapeutic dose does not affect the blood-pressure, but, contrary to the statements of Seibert, Max Quehl, and Bourgeois, it has been shown by Harnack and by Reichert that the toxic dose does lower the arterial pressure and is a direct paralyzant of the cut-out frog's heart. Reichert has shown that the mammalian heart is similarly affected by the drug, and the final fall of pressure must be at least in part of cardiac origin. Reichert states that preceding the fall of pressure there is a distinct rise, which is prevented by previous section of the cord, and is, therefore, probably due to stimulation of the vaso-motor centres. The pulse-rate is markedly increased by small and large doses of apomorphine, the maximum usually being reached about the time vomiting is fairly established; subsequently, in poisoning, the pulse falls below normal. Reichert believes the rise to be due to stimulation of the accelerators, and the fall to the influence upon the heart-muscle.

*Respiration.*—Usually the respiration-rate is increased by decided or toxic doses. During the convulsive period of the poisoning the respirations become irregular and unequal, and they finally grow more and more shallow and infrequent, until death results from a paralysis of the respiratory centres. Both Harnack and Reichert have noted that in the rabbit previous section of the par vagum does not prevent, but rather increases, the respiratory acceleration; Reichert affirms that in the cat and dog no increase of the respiration-rate occurs under the action of the drug if the pneumogastriacs have been cut.

*Temperature.*—The action of apomorphine upon the temperature appears to be very trifling and inconstant. According to Ziolkowski, the bodily heat usually falls after large doses from  $0.1^{\circ}$  to  $0.5^{\circ}$  C. Moerz noticed in one man that the temperature rose during the vomiting  $0.2^{\circ}$ ; while Bourgeois affirms that in man the drug has no influence over the temperature, and Reichert has seen in animals a rise follow the hypodermic but not the intravenous injection of the alkaloid.

*Emesis.*—Gee was the first to announce that apomorphine is a certain and prompt emetic, producing but little nausea, and having the great advantage of acting in very small dose, a tenth of a grain being sufficient, when injected under the skin, to cause vomiting in ten minutes. The time required for action depends largely upon the

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\* The only one who has carefully studied them is Reichert, and his published account is self-contradictory. He reasons that the convulsions are chiefly spinal, and yet says that in mammals, after section of the spinal cord, except "in very exceptional cases," they are confined to the anterior part of the body.

amount of the drug exhibited. After very small doses twenty minutes may elapse; and in Bourgeois's experiments 0.45 grain produced violent vomiting in less than two minutes. After these large doses the emesis usually recurs once or twice at intervals of a quarter to half an hour. The vomiting seems to be of centric origin, as Reichert has succeeded in producing it when the thoracic aorta was tied so as to prevent any of the poison from reaching the stomach.

**Therapeutics.**—Apomorphine is a safe and reliable emetic, and may be used whenever it is desired simply to empty the stomach. Apomorphine has a tendency in bronchitis to cause free secretion, and is especially useful in the *suffocative catarrh* of infants, when an emetic is required to get rid of the bronchial exudation. Under these circumstances it is said not only to act efficiently as an emetic, but also to render the mucus more copious and fluid. In the "drunk wards" of some of the Philadelphia hospitals for the relief of *acute debauch* apomorphine is preferred because the subjects habitually go to sleep directly after the vomiting ceases. Tull has found it useful in acute *chorea*.

Probably because it has morphine in its name there was at one time a rather wide-spread belief that apomorphine was not a suitable emetic in narcotic poisoning. In fact, however, narcotics influence the action of apomorphine only as they do that of every other emetic, and if apomorphine has any narcotic influence it does not interfere with its emetic action. Apomorphine may, therefore, be used in any poisoning: hypodermically given, it is often especially useful as a reinforcement of a mechanical emetic exhibited by the mouth.

**Administration.**—As an emetic, apomorphine has usually been administered hypodermically, in doses of one-tenth of a grain (0.006 Gm.), repeated every ten minutes until some effect is induced; but it may be exhibited by the stomach in double the amount. In cases of severe poisoning, where time is of great moment, it may be well to give as much as one-fourth of a grain (0.016 Gm.) at a single injection. In feeble persons, however, caution must always be exercised in using it, as one-fifteenth of a grain has caused death in seven minutes in an adult, fifty-four years old, suffering from chronic bronchitis with marked emphysema.\* The expectorant dose is one-sixteenth of a grain (0.004 Gm.). Care must be exercised in its use in children. Loeb gave hypodermically 0.03 grain to an infant, thirteen months old, suffering from capillary bronchitis: the free vomiting which was induced left the infant much exhausted. In a very few cases apomorphine has failed to vomit, and even caused startling symptoms: so that care should be exercised not to push the remedy too far. Carville affirms that three-tenths of a grain has caused a syncopal condition in an adult, and Prevost details a case in which syncope and threatening collapse were apparently induced by a very small dose. In children especially must care be exercised, since, according

to Harnack, the drug is very liable to produce collapse. Greenish preparations of apomorphine should not be used unless the dose be very small. Constantine Paul states that if glycerin be used as the sole menstruum the solution will keep three or four days. Carville affirms that glucose acts well as a preservative, and it is also asserted that a few drops of muriatic acid will suffice.

**MECHANICAL OR REFLEX EMETICS.**—The only drugs of practical value in this group are ground mustard and zinc sulphate; copper sulphate being so irritant as to be dangerous, and alum and other drugs sometimes used too uncertain in their influence.

*Mustard flour* is very prompt and even violent in its action, and is to be used when it is desired simply to evacuate the stomach rapidly. As it is generally to be had at once, it is especially useful in such emergencies as *narcotic poisoning*. Dose, a heaped tablespoonful in half a pint of water, repeated, if necessary, in ten minutes.

*Zinc sulphate* is a very sure emetic, much used in narcotic poisoning, especially with ipecacuanha or apomorphine. Dose, thirty grains (2 Gm.) dissolved in about two ounces of water: it may be repeated in fifteen minutes, if necessary.

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### FAMILY III.—CATHARTICS.

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THE question whether the cathartics cause movement of the bowels by increasing the intestinal secretions or the peristaltic activity has been much discussed.

The methods which have been most used for investigating the action of drugs upon the intestinal secretions are those of Thiry and of Moreau. Thiry's method consists in drawing out a knuckle of intestine and making a fistulous opening through the skin, closing

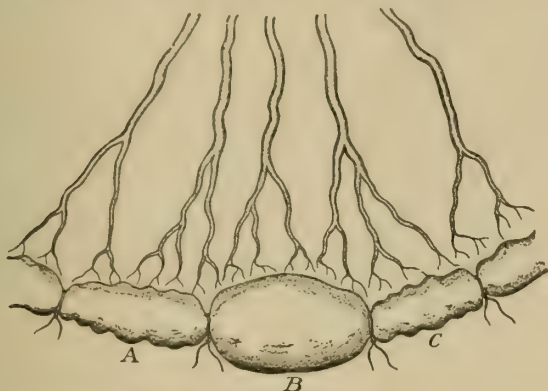


FIG. 18—MOREAU'S EXPERIMENT.

Three loops of intestine are tied off. Into B is injected the cathartic and the intestine returned to the abdomen. After a time loop B is found to be distended with fluid while A and C are not.

the other end of the piece of intestine and uniting the ends of the main portion of the intestine so as to reform a continuous tube, leaving a *cul de sac* which can be studied through the fistulous opening. The method of Moreau consists in tying off a loop of the intestine into three portions, in the central one of which the tract is injected and its fluid content compared with the ligated piece on either side which are taken to indicate the normal secretory rate of intestinal fluid. To determine the muscular activity of the intestines peristaltic movements may be directly observed, the animal being immersed in a warm physiological salt solution; or the rate of passage of fecal matter or foreign body may be observed; or an inflated rubber balloon may be inserted into the intestines communicating with a Marey tambour and the compression of the balloon being taken as an index of peristaltic activity.

The results which have been achieved by these methods of study are so absolutely contradictory as to make direct conclusions con-

cerning the mode of action of cathartics almost impossible. The causes of this confusion in results we believe are three. In the first place, a large number of observers have considered that all cathartics act in the same manner. It seems to us absurd to take it for granted that substances differing so widely in their chemical composition, in their general physiological effects, and the clinical results from their use, as sodium sulphate, aloes and croton oil act in the same manner on the intestines. The second reason of failure is the variance from natural conditions in many of the methods of experimentation. Finally it must be remembered that the alimentary tract of both dog and rabbit are functionally very different from the human intestinal canal.

As we believe that the vegetable cathartics act differently from the salines we deem it wiser to consider their actions separately under their respective heads rather than to go into a detailed description of the confusing results which have been obtained with the cathartics in general.\*

The indications to fulfil which cathartics are used, are as follows:

1. *To unload the Bowels.*—It is not necessary, in a work like the present, to say anything about the evil results of retained fecal matter, but only to point out the methods of relief. Before this can be done to advantage, however, a summary of the causes of *constipation* is required. Constipation may be well divided into acute and chronic. *Acute* or *temporary constipation* is that which occurs under special, transient circumstances, as in convalescence from acute disease, and in pregnancy. It is to be relieved by the use of laxative articles of diet, and, this not sufficing, by laxatives or purgative medicines. It should never be forgotten that acute constipation is sometimes due to organic affections of the alimentary canal, such as enteritis or intussusception, or is caused by mechanical obstacles, such as a hard foreign body or an enormous gall-stone. It is evident that such cases are not simple constipation,—that the treatment required is essentially different from that of the latter affection, and is various according to the lesion. For the diagnosis and treatment of these diseases the reader is referred to works on the practice of medicine. *Chronic constipation* may be due to sedentary habits of life; to habitual overwork, especially of the nervous system; to a deficiency of intestinal secretion and of peristalsis, apparently natural to the individual and without obvious cause; to long-continued voluntary habit of restraining the desire to go to stool; to lead or other forms of poisoning; and to diseases of the nervous system producing a paralytic state of the intestinal muscular fibres. It is evident that in the treatment of these various forms of constipation due regard must be paid to the cause, which should always, if possible, be removed. There are also certain cardinal principles which apply to the treatment of all forms of chronic constipation. They are as follows:

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\* For a consideration of the effects of drugs upon the biliary secretion see page 514.

A voluntary effort at defecation is to be daily made at a fixed hour, whether the desire exists or not.

Medicines are to be avoided as far as possible, a sustained effort being made to regulate the bowels by means of diet.

In very many cases the daily use of enemata of cold water, with attention to diet, suffices to attain the desired result.

If medicines become necessary, as small an amount as will suffice, and the mildest drugs, are to be used. Purgatives or laxatives are at best merely temporary devices, and if abused in costiveness increase the trouble. So far as can be, the attempt should be to produce a permanent impression, an alteration of the intestinal glandular action or peristalsis. Thus, when atony of the muscular coat exists, strychnine, or, according to comparatively recent experiments and clinical observations, physostigma may be employed; if the hepatic or other glands are habitually torpid, nitro-hydrochloric acid may be administered.

When constipation is attended by low spirits and a coated tongue, it is almost always due to a deficiency of secretion, and may be looked upon as a form of dyspepsia: in such cases nitro-hydrochloric acid is especially valuable, but sometimes a mild mercurial course seems almost imperative.

A second use of cathartics under the present indication is to remove offending materials, as indigestible or irritant food, foreign bodies, acrid discharges, etc. In many cases of indigestion with undue fermentation in the alimentary canal a brisk cathartic does great good by producing the expulsion of micro-organisms. The possible importance of this is shown by the experiments of Gilbert and Dominici, who found that a single dose of a saline caused in a healthy man the expulsion of over four hundred and eleven billion organisms.

2. *To deplete.*—On account of the large serous flow which they produce, the hydragogue cathartics when freely exhibited cause a very decided general depletion.

Local depletion by means of cathartics is called for in *congestion of the portal circulation*, as well as in *dysentery* and other acute intestinal inflammations. Under the first of these conditions may, we think, be included without violence cases of so-called *torpidity of the liver*, which will be discussed in the article upon mercurials (p. 513). In *acute intestinal inflammations* the salines are to be preferred when depletion is desired, as they produce large serous discharges and are not irritant.

3. *To promote Absorption.*—By emptying the blood-vessels the cathartics favor the absorption of the exuded fluid in general dropsy. For this purpose the hydragogues, and especially elaterin, are the best purgatives. The production of catharsis is the surest method of relief in general *dropsy*, also in *ascites*; in other forms of local effusion its effects are less marked. As, however, purgation is the most exhausting of all the plans employed for the cure of dropsy, due regard must always be had to the strength of the



patient. It is frequently necessary actively to support or even to stimulate while it is being carried out.

4. *To revulse*.—The long tract of the alimentary canal affords a great extent of surface upon which to practise revulsion in certain brain diseases, as in *mania* and rheumatic or gouty *irritation of the cerebrum*. In *hyperemia* of the brain, purgatives do good by depleting as well as by acting as revulsives. The drastics should be preferred.

5. *To eliminate*.—It cannot be doubted that the use of purgatives in such diseases as fevers and cholera, with the idea of eliminating some *materies morbi*, rests simply upon a crude, unproved, and probably false pathology. In *rheumatic disease* and in *gout* it is more probable that they do good in this way, although it is by no means certain that the advantage derived from their use is not simply due to depletion. In cases of retained renal secretion, the evidence is very decided that they do aid in expelling the products of retrograde metamorphosis.

**Enemata**.—When it is desired simply to unload the lower bowels, the object can often advantageously be attained by injecting various materials into the rectum, so as, by mechanical distention or by irritating the mucous membrane, to stimulate the peristaltic action. The simplest, least irritant, and least active *enema* is one of cold water. In cases of habitual *constipation*, especially when complicated with *piles*, the injection of a pint of cold water at a fixed hour daily often acts most kindly. The ordinary "opening injection" consists of a pint of water and a tablespoonful, each, of salt, molasses, and soft soap; castor oil is often added to it, and, if it be desired to make it very active, a teaspoonful of oil of turpentine.

*Large Enemata*.—Except in individuals of extreme nervous irritability, there is little difficulty in filling the large intestine with water, and sometimes the fluid can even be made to enter the small intestine. The greatest gentleness should always be practised, a forcing syringe never being used. The apparatus should consist of a rectal tube, and an ordinary india-rubber tube, four feet long, fitted to the rectal tube and to a funnel, india-rubber bag, or other receptacle. The patient should lie upon his back with the hips elevated, or in the knee-chest position, so that the pelvis may be much higher than the shoulder. The rectal tube having been introduced into the rectum, the end with the receptacle containing water is to be raised vertically. It is essential that the tube be fitted with a cock, or be pinched, so as to regulate the passage of the liquid. In this way from five to nine pints are readily injected. Unless it is especially desired to get the effect of cold or heat upon the intestine, the water in the receptacle should be about 100° F.

Large enemata are especially valuable as affording a means of locally treating the intestines. Very frequently in *dyspepsia*, *chronic constipation*, and other functional diseases of the digestive organs, the large intestine habitually contains scybala, fecal matters, acrid secretion, or other irritant substances, whose removal two or three

times a week by means of simple water or water impregnated with half a drachm of sodium bicarbonate to the quart brings great relief. In *dysentery*, chronic or acute, and in *pseudo-membranous colitis* or *enteritis*, by means of the large enemata, local application can be made to the colonic mucous membrane. In this way, in acute *dysentery*, water, antiseptics, germicides, bismuth subnitrate, and other appropriate remedies can be used. In chronic dysentery, one drachm of silver nitrate dissolved in half a gallon of water is often of the greatest service.

As originally recommended by Mosler, these injections are sometimes very useful against intestinal parasites. In this way especially may they be used against the *oxyuris vermicularis*, which often inhabits the whole of the large intestine. In bad cases of *seat-worm*, the large injection should always be employed. In obstinate cases of *tape-worm*, when the worm has been weakened, and partially or completely expelled from the small intestine under the influence of vermifuges given by the mouth, filling the colon with a medicated solution often brings success. Sometimes a saturated solution of salt suffices, or quassia may be employed. Mosler records as especially effective a tablespoonful of chlorine water to every pint and a half of water. A. Röhrig having found that intestinal injections of water have a very great influence over the secretion of bile, Mosler has been led to try forced enemata in *catarrhal* and other *jaundices*, with asserted good results.

**Hypodermic Purgation.**—Although several substances are capable of producing purgation when injected hypodermically, *Apocodeine* is the only known substance which appears to have practical value. It seems to be moderately effective, producing soft but not numerous or very watery stools: it is probably not effective when the constipation is obstinate, and not sufficiently drastic or hydragogue in its action to be of value in cases of severe diseases of the brain when counter-irritation through the intestinal tract may be desired. From one-third to one grain (0.02–0.06 Gm.) of the hydrochlorate may be injected with proper antiseptic precaution.

According to W. E. Dixon, *podophyllo-toxin* given hypodermically purges actively, but produces severe local inflammation and sloughing at the point of injection. Apparently the first to notice that apocodeine had the power of increasing intestinal peristalsis was Guinard. After him, Toy determined that when it was given by the mouth or hypodermically it acted as a laxative; and Raviart and Bertin in a number of cases found the injection of thirty minims (2 C.c.) of a one-per-cent. watery solution of apocodeine hydrochlorate produced soft stools without any other disturbances except some pain and diffused redness at the place of injection. W. E. Dixon determined by experiments upon the lower animals that apocodeine lessens blood-pressure by dilatation of the blood-vessels and increases intestinal peristaltic action. Heinze has used the remedy in a large number of cases. He finds the dose of 2 C.c. of a one-per-cent. solution is usually insufficient, and that the strength of the injection may be increased to two or even three per cent.; and in the latter dose is almost certainly effective, in some cases the effect continuing several days. No narcotic influence was perceptible, but in a number of cases there was distinct irritation at the place of injection.

Fronmüller says that one to three grains of Merck's aloin dissolved in hot water, administered hypodermically, act as an efficient purge; R. Kohn states that in his hands aloin of three different commercial varieties, hypodermically administered in ten times the dose employed by Fronmüller, failed to act. In 1881, as the result of an elaborate investigation, A. Hiller reached the conclusion that while there are four purgatives,—namely, aloin, cathartic acid, and the pure colocynthin and citrullin of Merck,—which are capable of purging when given hypodermically, they are all too irritant for practical use; a conclusion which was confirmed by Kohlstock. According to Meyer, the irritant action of Barbados aloin is largely due to the precipitation in the subcutaneous tissue of insoluble and extremely irritating crystals of the drug, and may to a considerable extent be overcome by the use of formamide as a vehicle.

**Laxative Foods.**—As has been already stated, constipation should always, when possible, be overcome by laxative food. There are two qualities by virtue of which food is laxative. Chief of these is *bulk*. All aliment which contains a large amount of innutritious material affords a large residuum, which, by distending the intestine, stimulates peristalsis. Contrariwise, articles of diet which are highly nutritious and afford but little residuum are constipating. This holds good, more or less strictly, among the lower animals. Thus, the flesh-eating carnivora are habitually constipated, the grass-eating herbivora very generally lax.

Owing to its containing so little of the innutritious portion of the grain, the finest white flour favors a costive habit, while the "cracked wheat," in which the whole grain is eaten, is laxative,—as to a still greater degree is bran, which is composed almost wholly of the husk of the wheat, the least nutritious portion of it, and therefore leaves a large residuum after digestion. *Cracked wheat* is boiled into a sort of jelly-like mass, and eaten with cream and sugar, while *bran* is taken in the form of bran bread, bran crackers, or bran mush. *Unbolted flour*, containing the whole of the grain, is about equal to cracked wheat, and is often made into bread. *Indian meal*, in the form of cakes or of mush, is highly nutritious and somewhat laxative; *oatmeal* is decidedly laxative, scarcely so much so as bran, but much more nutritious. When it agrees with the stomach, and is digested, it is probably the best of all these laxative articles of food. As the oats produced in southern climates are very inferior, care should be taken to procure oatmeal manufactured from Northern grain. It should be thoroughly cooked, and is best eaten in the form of a thick porridge. In dyspepsia all of these articles sometimes disagree with the stomach and cannot be used.

Some dietary articles seemingly possess *dynamic* laxative powers,—*i.e.*, they exert a direct action which is not mechanical, but is similar to, although far less active than, that of the true purgatives. They intensify the intestinal action. Chief among substances of this class are *molasses* (SYRUPUS FUSCUS) and its congener, *brown sugar*; *white sugar* (SACCHARUM, U. S.) probably does not share these laxative powers; *sugar of milk* (SACCHARUM LACTIS, U. S.) is probably also nearly inert. Of course, great care is usually necessary in taking advantage of the laxative virtue of molasses, on account of the danger of producing fermentation and acidity in the primæ viæ.

There are certain foods which combine the two methods of action spoken of, chief among which are fresh acidulous fruits, such as apples, pears, etc., and dried fruits. Of the latter several are recog-



nized by the Pharmacopœia, including the *fig* (FICUS), the *prune* (PRUNUM), and the *tamarind* (TAMARINDUS), and the pulp of the *Cassia fistula*. Besides these should be mentioned as containing similar properties, *manna*, which is the exudation of the European ash, *Fraxinus ornus*, and contains a saccharine principle, mannite, to which apparently it owes its laxative properties as well as its sweet taste.

Among constipating articles of diet, it is only necessary to call attention to milk as one of the most decided of the class.

The purgatives have frequently been divided, according to the severity of their effects, into laxatives, purgatives and drastics. As the difference, however, is frequently a question of dosage and takes no cognizance of certain marked pharmacological relations, the following division appears to us to be more scientific and at least equally as valuable from a clinical standpoint:

Purgatives containing derivatives of anthraquinone,—rhubarb, senna, cascara sagrada, frangula, and aloes.

Vegetable cathartics containing resinous glucosides and acids,—this includes most of the so-called drastics, as jalap, podophyllin, colocynth, scammony, and gamboge; also the more mildly acting euonymus.

Cathartic oils,—castor oil, croton oil.

Salines,—the salts of sulphuric, phosphoric, citric and tartaric acids.

Mercurials.

### FIRST GROUP.

A number of vegetable laxatives contain derivatives of anthraquinone [ $C_{14}H_8O_2$ ] to which they owe, at least in part, their laxative properties. Among these principles the most important, which have so far been isolated, are emodin—trioxymethyl-anthraquinone [ $C_{14}H_4(CH_3)(OH)_3O_2$ ] and chrysophanic acid, dioxymethyl-anthraquinone [ $C_{14}H_5(CH_3)(OH)_2O_2$ ]. The most prominent plants containing anthraquinone derivatives are rhubarb, senna, aloes, cascara sagrada and frangula. It is to be noted, however, that these plants appear to contain other bodies which aid their aperient properties, and that the pure principles are frequently less purgative than crude drugs, perhaps for purely physical reasons.

The anthraquinone derivatives seem to cause catharsis by a direct irritant influence upon the intestine, leading, thereby, to some increase in the fluid constituents of the bowel, but chiefly hastening peristalsis. This irritation, it should be noted, is never severe enough, even after large doses, to give rise to serious inflammation such as may be caused by the drastics. It does, however, contraindicate the use of this group as purgatives in cases of enteritis.

### RHUBARB.

The dried rhizome of *Rheum officinale*, Baillon, and other species of *Rheum* growing in China, and Thibet.

The rhubarbs are large perennial herbs with leaves two to four feet long; the leaves of one species being used in this country as a food stuff.

Rhubarb occurs in hard, irregularly cylindrical or roundish bits, of a brownish-yellow color, with a pleasant aromatic odor and a peculiar bitter taste, imparting to the teeth a sense of grittiness due to the presence of a number of minute crystals of calcium oxalate.

It contains besides *emodin*, a glucoside, *chrysophan*, which yields on decomposition *chrysophanic acid*. There is also present a notable proportion of tannin.

#### Official Preparations :

Extractum Rhei.....	5 to 10 grains (0.3-0.6 Gm.).
Pilulæ Rhei Compositæ (Each 2 grains Rhubarb and 1½ grains Aloes).	
Pulvis Rhei Compositus (Rhubarb 25 per cent., with Magnesium Oxide and Ginger).....	½ to 1 drachm (2-4 Gm.).
Fluidextractum Rhei.....	15 to 30 minims (1-2 C.c.).
Tinctura Rhei (20 per cent.).....	1 to 2 fluidrachms (4-8 C.c.).
Tinctura Rhei Aromatica (20 per cent.).....	1 to 2 fluidrachms (4-8 C.c.).
Mistura Rhei et Sodæ (1½ per cent.).....	½ to 1 fluidounce (5-30 C.c.).
Syrupus Rhei (10 per cent.).....	2 fluidrachms (8 C.c.).
Syrupus Rhei Aromaticus (3 per cent.).....	4 fluidrachms (15 C.c.).

**Physiological Action.**—Rhubarb is somewhat stomachic, tonic, actively purgative, and, owing to its tannic acid, secondarily astringent, leaving a decided tendency to constipation after the primary purgation. Owing probably to its chrysophanic acid, it gives a yellowish color to the milk of nursing women and to the urine. Rhubarb urine is to be distinguished from that of jaundice by its becoming purplish-red on the addition of an alkali.

**Therapeutics.**—Notwithstanding its astringent property, rhubarb is largely used as an habitual laxative, because it does not impair, but, on the contrary, seems to strengthen, the appetite and the digestion. It should not be used in a high sthenic state of the system, or when depletion is necessary, but is very valuable when it is desired simply to unload the bowels in a debilitated subject. It is much used in *diarrhæa*, with intestinal weakness or relaxation, to unload the bowels of acrid secretions. The *aromatic syrup* combined with an alkali is especially serviceable in the *summer bowel-complaints* of children when the stools are greenish and mucous.

#### ALOES.

Aloes appears to have been produced in the Island of Socotra, as far back as the time of Alexander the Great, 333 B. C.; and the U. S. Pharmacopœia of 1890 recognized Socotrine and Barbados aloes, besides which a variety of aloes produced at the Cape of Good Hope, Cape aloes, largely occurred in commerce. At present, under the general name of Aloe, the Pharmacopœia recognizes simply aloes, allowing the pharmacist to use any form of aloes which conforms to the standard given in the text of the Pharmacopœia. Aloes is not now produced at Barbados, while the Socotrine aloes occurs in the American market only in small quantities, the mass of the commercial drug being produced in the Island of Curaçoa.

Aloes is obtained by cutting off the thick, succulent leaves of various species of the genus *aloe*, allowing the juice to drain into skins, troughs, or other vessels, and afterwards inspissating either by exposure to the sun or by means of artificial heat. The aloes are blackish-brown or yellowish-brown, of a bitter, nauseous taste, often with a smooth fracture, and in the best varieties with garnetty edges; they yield their virtues to alcohol, imperfectly to water, and very imperfectly to alkaline solutions.

T. and H. Smith in 1850 discovered in Barbados aloes a crystalline principle,—*aloin*,—which was shortly afterwards found by Pereira to exist already crystallized in the sap of various species of *aloe*-plants, and was subsequently obtained by Groves from Socotrine aloes. *Aloin* crystallizes from its aqueous solution in sulphur-yellow granules, from a hot alcoholic solution in star-like groups of needles. It is neutral, almost odorless, of a taste at first sweetish, afterwards intensely bitter; is soluble with difficulty in cold water, freely in boiling water and in alcohol. There are three varieties of *aloin*,—*barbaloin*, *socaloin*, and *nataloin*, obtained respectively from the Barbados, the Socotrine, and the Cape aloes. *Aloinum*, U. S., is the *aloin* derived from Barbados aloes or from Socotra or Zanzibar aloes. The *aloin* of commerce is chiefly *barbaloin*, and is certainly an active cathartic in doses of half a grain to a grain (0.03–0.06 Gm.).

H. Meyer finds that the Barbados and Curacao *aloin* act both on man and on many lower animals as a purgative, while the Natal *aloin* fails ordinarily to affect man, although it is a certain cathartic in dogs and cats. The time required for the Barbados *aloin* to produce purgation was from eight to thirty hours, which Meyer believes to be due to the fact that its physiological action depends upon its undergoing chemical change in the intestines. In order to facilitate this change he exhibited with it potassium carbonate and ferrous sulphate, and found that these salts markedly hastened the effect. He also found that Natal *aloin*, when given to persons who had been fed for six days an exclusively animal diet, acted as a cathartic.\* In the lower animals Kohn found the hypodermic injections of *aloin* to cause gastro-enteritis with albuminous urine, and a peculiar inflammation of the kidneys; 0.1 gramme of Merck's *aloin* for every kilogramme of bodily weight was a fatal dose for the dog. Brandenburg has experimentally shown that very large doses of *aloin* cause in the rabbit a fatal necrosis of the renal epithelium; small doses produce a parenchymatous nephritis.

#### Official Preparations:

Aloe Purificata.....	4 to 10 grains (0.3–0.6 Gm.).
Aloinum.....	$\frac{1}{2}$ to $\frac{1}{2}$ grain (0.01–0.03 Gm.).
Extractum Aloes.....	1 to 3 grains (0.06–0.2 Gm.).
Pilulæ Aloes (2 grains).....	2 to 4 pills.
Pilulæ Aloes et Ferri (1 grain).....	2 to 4 pills.
Pilulæ Aloes et Myrrhæ (2 grains).....	2 to 4 pills.
Pilulæ Aloes et Mastiches [Lady Webster Pill ](2 grains).....	(2 to 4 pills).
Pilulæ Laxativæ Compositæ—[A. B. S. Pills] ( <i>aloin</i> $\frac{1}{2}$ grain).....	1 to 2 pills.
Tinctura Aloes (10 per cent.).....	1 to 3 fluidrachms (4–12 C.c.).
Tinctura Aloes et Myrrhæ (10 per cent.)....	1 to 3 fluidrachms (4–12 C.c.).

\* Consult *Trans. Brit. Pharm. Soc.*, 1872; *Brit. Med. Journ.*, 1887, i. 747; *Bull. Thérap.*, xci. 259. *Lond. Med. Record*, 1877, 459; and *Edin. Med. Journ.*, xx. 1002.



**Physiological Action.**—Aloes is a stomachic, stimulant cathartic, remarkable for the slowness of its action. It has been supposed to influence chiefly, if not solely, the large intestine, and the clinical evidence is very strong that in overdoses it produces irritation of the rectum. The belief, formerly universal, that it is capable of producing hemorrhoids, and the statements that its habitual use in large doses causes tenesmus, a feeling of weight, heat, and uneasiness in the pelvis, and occasionally excitation of the sexual organs, are of very doubtful correctness. Aloin has been detected in the urine by J. Dietrich, by Kohn and by Meyer.

**Therapeutics.**—Aloes, being a stimulating purgative, is chiefly used in the *constipation* of atonic subjects. In the constipation of plethora it should not be employed; neither should it be administered when active abdominal or rectal inflammation exists. During pregnancy it is best avoided, and large purgative doses should never be given. Formerly it was taught that aloes should not be used in *hemorrhoids*; but most, if not all, of the cases of this affection depend upon a condition of relaxation of the rectal veins, and Fordyce Barker insists upon the great value of aloes in piles, and states that Oppolzer was especially famous for his treatment of this affection, and that his prescriptions were, when piles are associated with constipation, aloes and quinine; without constipation, aloes and sulphate of iron. When costiveness accompanies atonic *amenorrhæa*, aloes alone of all the laxatives should be exhibited; and it is also of service in atonic *menorrhagia*.

### SENNA.

Under the name of Senna various species of the genus *Cassia* have found their way into commerce, but at present the U. S. Pharmacopœia recognizes only the leaflets of the *Cassia acutifolia* of Nubia and Upper Egypt (*Alexandria Senna*), and of the *Cassia angustifolia* of Southern India (*Tinnevelly Senna*). The senna-leaves vary from three-fourths of an inch to an inch and a half in length, and are to be distinguished by the inequality of their bases, the two sides of the lamina or leaf-blade joining the midrib at unequal heights and angles. Senna depends for its activity upon the presence of the glucosides chrysophan and emodin. *Cathartic acid* which has been described as its active principle is apparently not a pure principle.

#### Official Preparations:

Confectio Sennæ (10 per cent.).....	1 to 2 drachms (4–8 Gm.).
Pulvis Glycyrrhizæ Compositus (18 per cent.) ½ to 1 drachm (2–4 Gm.).	
Fluidextractum Sennæ.....	½ to 1 fluidrachm (2–4 C.c.).
Syrupus Sennæ (25 per cent.).....	1 to 4 fluidrachms (4–15 C.c.).
Infusum Sennæ Compositum (Black Draught)	
(6 per cent.).....	4 to 6 fluidounces (120–180 C.c.).

**Therapeutics.**—Senna is a very powerful, somewhat irritating hydragogue cathartic, acting, it is said, as readily upon swine, dogs, cats, and horses, as upon man. When given alone, it is very apt to

gripe severely, and is consequently more often used in combination. In obstinate *fecal accumulation* the Black Draught constitutes a most efficient and safe remedy.

In small doses it is often used as a laxative. Its infusion injected into the veins is said to cause both vomiting and purging, and the milk of nursing women taking it is affirmed to act as a cathartic. An aromatic should be administered with senna, to lessen its tendency to gripe. The confection is a very complex but elegant preparation, used only as a laxative, especially in *pregnancy*; it is not suited to dyspeptic cases, on account of its tendency to derange the digestion. The compound infusion contains manna and magnesium sulphate, causes very large watery discharges in dose of four fluidounces (120 C.c.), and is often used in *fecal impaction*.

### RHAMNUS.

Two species of the genus *Rhamnus*, the *Rhamnus Frangula* or buckthorn, and the *Rhamnus Purshiana*, California buckthorn, are recognized by the Pharmacopœia. The former, however, is but little used in this country. The California buckthorn is a small tree which is found on the Pacific coast from California to Oregon. The official portion of the plant is the bark which is commonly called *Cascara Sagrada* (Sacred bark). It is one-sixteenth to one-eighth of an inch thick and usually occurs in the form of quills from two to four inches long. The outer surface is gray, the inner surface brown. The taste is bitter and nauseous. Its activity is due to a glucoside variously known as *purshianin* or *cascarin*, which yields on decomposition emodin. The bark, when fresh, also contains a ferment which causes much griping. The Pharmacopœia, therefore, directs that it should at least be one year old before being used.

#### Official Preparations:

Extractum Rhamni Purshianæ.....	2 to 5 grains (0.12–0.3 Gm.).
Fluidextractum Rhamni Purshianæ.....	$\frac{1}{2}$ to 2 fluidrachms (2–8 C.c.).
Fluidextractum Rhamni Purshianæ Aromati-	
cum.....	$\frac{1}{2}$ to 2 fluidrachms (2–8 C.c.).
Fluidextractum Frangulæ.....	15 minims (1 C.c.).

*Cascara sagrada* differs from most of the cathartics in the fact that there is apparently no tendency to constipation consequent to its use; on the contrary, it frequently seems to act as a tonic to the bowel, restoring its motor function and is, therefore, frequently employed as a laxative in *habitual constipation*.

**PHENOLPHTHALEIN.**—This substance which has long been familiar to chemists, as an indicator for alkalies, has been recommended by Tunnicliffe and others as a pleasantly acting laxative. In doses of from 2 to 5 grains (0.1–0.3 Gm.) it causes large mushy stools without much griping.

If used too freely it is not entirely devoid of toxic properties.

**BILE.**—The United States Pharmacopœia recognizes crude *Oxgall*, the fresh bile of *Bos taurus*, and prepares from it by means of alcohol *FEL BOVIS PURIFICATUM* (*Purified Oxgall*), a yellowish-green, soft solid, having a peculiar odor, and a partly sweet and partly bitter taste. It is very soluble in water and in alcohol.

There is much experimental evidence to show that oxgall is the most powerful stimulant we have to the secretory activity of the liver. Schaeffer, however, believes that this substance does not have a direct stimulant action upon the liver but that its effects are due simply to the offering for absorption a preformed constituent of the bile, because he found that the amount of bile solids passed out after the exhibition of oxgall did not exceed the normal plus the amount which had been artificially exhibited.

When taken internally, in large doses, it is a feeble laxative and there is some clinical evidence in favor of the belief that, in that condition known as *chronic biliousness*, full doses of oxgall often act very favorably. We have also used it in *catarrhal jaundice* with apparent excellent results. Dose, five to twenty grains (0.3–1.3 Gm.).

### SALINE CATHARTICS.

Under the term of salines are included certain salts of the earthy metals, which because of their slight absorbability from the intestinal tract disturb the osmotic balance between the bowel contents and the surrounding tissues. In the majority of instances the ion determining the cathartic action is the acid radical, although certain bases, notably mercury and magnesium, seem to possess cathartic properties. The laxative salts are those of sulphuric, phosphoric, citric and tartaric acids. The official salts of this class are: sodium sulphate, phosphate, and citrate; magnesium sulphate and citrate; sodium and potassium tartrate; potassium citrate and potassium bitartrate.\*

#### Official Saline Cathartics:

Magnesii Sulphas [Epsom Salts] . . . . .	4 drachms (15 Gm.).
Magnesii Sulphas Effervescens (50 per cent.) . . . . .	1 ounce (30 Gm.).
Sodii Sulphas [Glauber's Salt] . . . . .	4 drachms (15 Gm.).
Sodii Phosphas . . . . .	1 to 2 drachms (4–8 Gm.).
Sodii Phosphas Effervescens (20 per cent.) . . . . .	4 drachms (15 Gm.).
Sodii Phosphas Exsiccatus . . . . .	$\frac{1}{2}$ drachm (2 Gm.).
Potassii et Sodii Tartras [Rochelle Salt] . . . . .	2 to 4 drachms (8–15 Gm.).
Potassii Bitartras [Cream of Tartar] . . . . .	$\frac{1}{2}$ to 1 drachm (2–4 Gm.).
Pulvis Effervescens Compositus [Seidlitz Powder] . . . . .	1 pair of powders.
Potassii Citras . . . . .	15 to 45 grains (1–3 Gm.).
Potassii Citras Effervescens (20 per cent.) . . . . .	1 drachm (4 Gm.).
Liquor Potassii Citratis (8 per cent.) . . . . .	$\frac{1}{2}$ to 1 fluidounce (15–30 Gm.).
Liquor Magnesii Citratis . . . . .	4 to 8 fluidounces (120–240 C.c.).
Liquor Sodii Phosphatis Compositus . . . . .	1 to 2 fluidrachms (4–8 C.c.).

\* The natural laxative waters, as those of Carlsbad, Saratoga Vichy, Kissingen, etc., are simply mixtures of these drugs with other salts, usually including large quantities of sodium chloride. (Formulæ for making these salts are in the National Formulary.)



The presence of one of these salts in the intestines, because it does not easily pass through the intestinal wall, not only prevents the absorption of water from the intestine but also encourages the passage of water from the surrounding tissues into the bowel by osmosis. It does not seem likely, however, that the pouring of fluid into the intestinal tract is the result solely, or even chiefly, of osmotic pressure, but that is still more dependent on a true stimulant influence on the intestinal glands. The investigations of Matthew Hay, although carried out many years ago, still remain the most probable expression of the mode of action of the saline cathartics. This author concluded that: 1. A saline purgative always excites more or less secretion in the intestines due to bitterness and specific properties of the salt rather than to osmosis; 2. the low diffusibility of the salt impedes the absorption of fluid; 3. between stimulated secretion on one hand, and lessened absorption on the other, there is an accumulation of fluid in the bowel; 4. the accumulated fluid partly from ordinary dynamic laws, partly from a gentle stimulation of peristalsis, reaches the rectum and produces purgation.

While there is some diversity of opinion as to which one of the factors involved in the catharsis is the most important, as far as the practical utilities of this group are concerned there is almost complete unanimity. The peculiar usefulness of the salines lies in their rapidity of action, their freedom from irritant properties and the liquid character of the stools produced.\*

Four theories as to the mode of action of the saline laxatives are extant. These are: First, that they act by increasing peristaltic activity; second, that they increase the fluidity of the intestinal contents by the process of osmosis; third, that they inhibit the absorption of fluid from the intestines, so making the contents more liquid; and fourth, that they directly stimulate the secretory activity of the intestinal glands.

The theory that the salines act solely by increasing the peristalsis is no longer tenable, for although Thiry, Radziejewski and Schiff fail to obtain an increase in the intestinal fluids after the administration of these laxative salts, the work of Moreau, of Brunton, of Vulpian, of Hay, and of McCallum, proves that there is an increase in the quantity of intestinal contents following the exhibition of these drugs.

That the augmentation of the fluid in the intestines is not due, at least entirely, to a change in the osmotic relation is shown, in the first place, by the fact that the comparative power of the various saline laxatives bears no relation to their endosmotic equivalent. Secondly, that concentrated solutions of sugar which have a much higher osmotic factor than the salines, do not purge, and thirdly that hypotonic solutions of these salts act cathartically.

The theory that these purgatives prevent absorption of fluid has been upheld by Schmiedeberg and his pupils, especially Wallace and Cushny. These authors found that when a solution of a sulphate, citrate or tartrate, approximately isotonic with the blood, was placed in a loop of intestine the fluid was absorbed much more slowly than a corresponding solution of chloride or iodide. This, however, does not show that a concentrated solution will not provoke a flow of fluid towards the intestines.

As regards the effect of the salines upon peristalsis, it is very difficult to draw conclusions. Le Gros, Van Braan Houckgesst and Rabouteau all assert that the salines do not increase the peristaltic movements of the bowel. Radziejewski finds

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\* For study of the effect of salines on metabolism see London Z. K. M., xiii.

that there is a greater peristaltic movement after the exhibition of Epsom's salts, and in the investigation of McCallum it was found that sodium citrate, sulphate, tartrate, phosphate, barium chloride and magnesium sulphate all produced an increase in peristalsis, even when injected subcutaneously or intravenously. Frankl was unable to confirm McCallum's claim that the salines purged after intravenous injection.

MAGNESIUM SULPHATE (*Epsom Salt*) ordinarily occurs in small, acicular, slowly efflorescent crystals, containing about fifty-one per cent. of water of crystallization, soluble in their own weight of water at ordinary temperatures. The taste is bitter, saline, and nauseous.

**Physiological Action.**—Epsom salt is a most active hydragogue cathartic, producing very large watery discharges without causing any irritation of the intestines.

Injected into the blood stream magnesium sulphate is a violent poison depressing the heart\* (Curci, Recke, Hay, and Matthews and Jackson), paralyzing respiration and producing anesthesia (Matthews and Jackson and Meltzer and Auer). According to Meltzer and Auer, when locally applied, it destroys the conductivity of nerve trunks. It has been injected into the subarachnoid space for the production of surgical anesthesia (Haubold and Meltzer). These effects are probably due to the magnesium ion.

Ordinarily magnesium sulphate is not absorbed from the intestines in sufficient quantities to produce any symptoms except purgation, but recorded cases show that the drug is capable of acting as a violent general poison. Christison reports a boy, ten years old, killed by two ounces, without the induction of purgation. W. Sang reports, as caused by four ounces of Epsom salt in a very concentrated solution, burning pain in the stomach and bowels, great dyspnoea, and collapse, with dilated pupils, muscular relaxation, and finally coma, ending in death, without purging or vomiting. In J. H. Neale's case the symptoms were violent enteritis, with most alarming heart depression, from which, however, the patient recovered.

Magnesium sulphate is very largely used when it is desired to deplete or to promote absorption through the bowels, as in *dropsies*; or to relieve congestion of the bowels themselves, as in *enteritis* or *colitis*; or when it is necessary to soften down *fecal accumulation*, as in obstinate constipation. M. Luton affirms that ten centigrammes (1.53 gr.), administered hypodermically, usually provoke several watery stools; but the practice seems to us a very doubtful one.

SODIUM SULPHATE (*Glauber's Salt*) occurs in six-sided, very efflorescent, striated prisms, which finally crumble into a white powder. It acts like magnesium sulphate, but is more powerful; it is, however, little used on account of its extremely nauseous taste. It is the chief active principle of many natural purgative waters which are so useful in chronic gastric and other abdominal catarrhs with constipation.

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\* According to Curci small doses elevate the blood-pressure by stimulating the vaso-motor centre.

The combination of two ounces of sodium phosphate, one-half ounce of sodium sulphate, and one-half drachm of potassium iodide, taken in full laxative doses, well diluted, upon rising, is often very efficient in such cases as are benefited by Carlsbad waters.

**SODIUM PHOSPHATE.**—The disodium hydrogen phosphate ( $\text{Na}_2\text{HPO}_4$ ) occurs in colorless, transparent crystals, which effloresce and become opaque on exposure. It is soluble in 5.5 parts of water, and has a saline taste, closely resembling that of common salt. In large doses it is a mild saline purgative, but as such is not at present very much employed. Sodium phosphate is a very useful remedy in chronic *infantile diarrhœa* with intestinal indigestion, especially as it occurs in bottle-fed subjects. It appears to have a specific action upon the liver and also upon the intestinal glands in general, so that it is often of great service where there are habitually chalky stools or white fluid motions, and in many cases of green stools. In *chronic hepatic torpor* and in *catarrhal jaundice* it is often used with great advantage, and it seems sometimes of value in *lithemia*.

In 1888 Haig affirmed, as the result of his experiments, that sodium phosphate has very pronounced effect in increasing the excretions of uric acid. In a subsequent paper, however, he stated that if the phosphate contain any sulphate, or if it be in the form of the acid phosphate, or meet with an acid in the stomach which should make it an acid phosphate, it has no power in increasing uric acid excretion; so that it seems to us that at present we cannot consider sodium phosphate as having distinct relations with uric acid excretion.

### TARTARIC ACID.

Tartaric acid occurs as a white powder or in large, hard, transparent, six-sided prisms, which are pyro-electric and phosphorescent when rubbed in the dark, are nearly free from odor, have a very sour taste, and are very soluble in water. In the shops the acid is almost always kept in the form of powder. Tartaric acid is the acid of the grape, and occurs in grape-juice as potassium bitartrate. When the juice undergoes fermentation and alcohol is developed, the acid salt, not being soluble in the newly formed menstruum, precipitates, collecting as a dark mass in the wine-casks, whence it is sent into commerce under the name of *argol* or *tartar*.

**Physiological Action.**—In powder or concentrated solution tartaric acid is a very decided irritant, capable of producing, when taken internally, violent œsophageal and gastric burning, vomiting, and, it may be, fatal gastro-enteritis.\*

Munch finds that when tartaric acid or citric acid is given it soon appears in the urine. H. Bence Jones has found that both citric acid and tartaric acid cause a pronounced increase in the acidity of the urine of persons taking them, and are apt

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\* Cases reported in the *Brit. Med. Journ.*, for June, 1893, in which the supposed dose was one hundred and eighty grains. Symptoms: diarrhœa, violent abdominal pains becoming more and more marked, followed by fever, delirium, and death on the seventh day. At the autopsy violent inflammation of the whole of the gastro-intestinal tract was found.



also to give rise to the presence of free uric acid in the excretion. Unfortunately, Jones did not attempt to determine whether the increased acidity was or was not due to the presence of the vegetable acid in the urine. It is probably partially burnt up in the body and partially eliminated by the kidneys.

Concerning the physiological action of the therapeutic doses of tartaric acid we have no definite information. General clinical experience, in accord with the experiments of Bobrick (quoted from Husemann), who found that very large doses render the heart's action weaker and slower, indicates that the drug is a very feeble cardiac depressant.

**Therapeutics.**—Tartaric acid itself is used only for the purpose of making effervescent salts, in combination with the bicarbonate of soda. The salts it forms with the alkalies are mildly cathartic, more gentle in their effects and more pleasant to take than the sulphates.

Potassium bitartrate is actively diuretic as well as cathartic and is considered among the diuretics (see p. 535).

POTASSIUM AND SODIUM TARTRATE (*Rochelle Salt*) is made by the addition of sodium carbonate to a solution of potassium bitartrate. It is soluble in 1.2 parts of water, and has a slightly saline taste. It is a mild saline purgative, decidedly less efficient, but much less offensive to the palate, than magnesium sulphate.

The most agreeable means of administering this salt is in the form of the *Seidlitz powder* (*Pulvis effervescens compositus*). This comes in two packets; the white paper contains about thirty-five grains of tartaric acid, the blue paper forty grains of sodium bicarbonate and two drachms of Rochelle salt. When they are taken, the powders are dissolved separately, the solutions added, and the whole drunk while effervescing. One pair of powders is the usual dose; but not rarely even two pair will fail to purge.

**Toxicology.**—There are, we believe, but three fatal cases of tartaric acid poisoning on record: one reported by Devergie, one by Taylor, in which death took place nine days after the ingestion of an ounce of the poison dissolved in half a pint of water, and one in which half an ounce of the acid was *supposed* to have been taken. The treatment of tartaric acid poisoning consists in the free exhibition of magnesia, of lime, of potassium or sodium carbonate, or of any article, such as soap, containing an alkali in a suitable shape, which may be at hand. The after-treatment is that of toxic gastro-enteritis.

### CITRIC ACID.

Citric acid is the acid of lemon- and lime-juice. It occurs in rhomboidal prisms, of a sour, almost corrosive, taste, extremely soluble in water. Lemon juice contains from seven to nine per cent. of citric acid.

#### Official Preparations:

Acidum Citricum.....	5 to 10 grains (0.3-0.6 Gm.).
Limonis Succus.....	$\frac{1}{2}$ to 1 fluidounce (15-30 C.c.).
Syrupus Acidi Citrici (1 per cent.).....	Used as a vehicle.
Liquor Magnesii Citratis.....	8 fluidounces (240 C.c.).
Potassii Citras.....	20 to 30 grains (1.3-2.0 Gm.).
Liquor Potassii Citratis (8 per cent.).....	$\frac{1}{2}$ to 1 fluidounce (15-30 C.c.).

**Physiological Action.**—Citric acid in concentrated form is actively irritant, but less so than tartaric acid. Serious poisoning by it is very rare, and we know of but one recorded fatal case (H. Kionka).

In Kionka's case, a girl in order to produce abortion took an unknown quantity of citric acid, and was brought dying into the hospital with the only clinical record that she had vomited greatly. Nine thousand four hundred and fifty-two grains of citric acid were collected from her gastro-intestinal tract. Marked evidences of violent gastritis were present, with gross evidences of hepatic degeneration. In the experiments of Maass citric, acetic, and tartaric acid were found to have very little influence on frogs unless in large quantities.

Hugo Schulz states that citric acid is an active antiseptic, a five-per-cent. solution being sufficient to preserve small pieces of meat for two weeks; one part in a thousand was fatal to paramecia.

**Therapeutics.**—*Lemon-juice* is a valuable remedy, but how or why it acts is at present entirely unknown. Neither citric acid nor any of its known salts act in disease as does the juice of the fruit. The chief and most important use of lemon-juice is in the cure and prevention of *scurvy*. During the disease three or four ounces may be given three times a day. As a prophylactic against the disease, lemon-juice is simply invaluable; but it is absolutely necessary that it be of good quality. In *acute rheumatism*, benefit may be derived from the free use of lemon-juice, as originally proposed by Rees, of London. One or two ounces of it may be given four or five times a day; but it is certainly less efficacious than the alkalies. In *catarrhal jaundice* and in *habitual torpor of the liver* the free administration of lemon-juice often aids in effecting a cure. In *fevers*, lemonade is a very refreshing and useful refrigerant drink.

The neutral citrates are the mildest of the group of saline laxatives. The only one which is used to any considerable extent as a laxative is the magnesium citrate, although both the sodium and potassium salt possess some laxative powers. (For a study of potassium citrate see p. 535.)

**SOLUTION OF MAGNESIUM CITRATE** is prepared by putting into a strong bottle a syrupy solution of magnesium citrate containing an excess of citric acid, adding potassium bicarbonate, and corking tightly. On account of its agreeable taste and effervescence, this preparation is much used as a purgative. It is similar to magnesium sulphate in its action, but is less efficient, more likely to gripe, and more irritating. It ought not to be used in inflammatory affections of the bowels.

### MERCURY.

The only preparations of mercury which are used as purgatives are *calomel* and *blue mass*. Of these the first is by far the more active, and indeed is the only one which can be relied upon to purge.

The chief interest in the purgative action of mercurials centres in the question as to their influence upon the liver. Clinically, there

seems no room for doubt that the mercurials, and perhaps some other cathartics, are capable of increasing the bile in the intestinal tract, especially in certain conditions, as that known as biliousness or hepatic torpor in which this excretion is lacking. As the whole trend of modern pharmacological investigation tends to show that the mercurial has no effect upon the liver to cause an increase in the secretion of bile, it is probable that the action of this group of remedies is a sort of mechanical one, perhaps to cause a contraction of the gall bladder and the expulsion of its contents into the intestinal tract.

It does not seem necessary to review in detail the large number of investigations concerning the action of drugs upon the flow of bile. A complete reference to the older literature upon this subject may be found in the 13th edition of this book. Suffice it to say, for the present purpose, that it seems to have been demonstrated by Stadelmann and his pupils that neither calomel nor any of the ordinary cathartics distinctly increase the secretion of bile.

As a result of much investigation and controversy it seems, to-day, well established, that the number of substances which produce an increased secretion of bile is comparatively small and does not include any of the cathartics. The most active stimulant of biliary secretion is bile itself. Sodium salicylate also seems well established as a biliary stimulant although inferior in power, and according to Kionka sodium benzoate and colchicin also increase the biliary flow.

The older investigations on this subject are open to serious objections. For instance, Rutherford, who found a marked increase in the biliary flow as a result of a considerable number of substances, mixed bile with his drugs to facilitate absorption, ignorant of the fact that the bile itself was a powerful stimulant to the secretory activity of the liver.

Rosenberg found that in dogs sodium salicylate increased the quantity and diminished the consistency of the bile; that turpentine had a slight stimulant power; while the Carlsbad salts seemed to decrease rather than increase the biliary flow. Neutral oils had a much greater power of stimulating biliary secretion than any other food or drugs, with the single exception of oxgall.

Stadelmann, in a series of apparently careful experiments on dogs, found that water, whether hot or cold, had no influence upon the amount or fluidity of the bile. Alkalies, including the sodium chloride, sulphate, bicarbonate, and phosphate, and many potassium salts, artificial Carlsbad salts, Epsom salts, and many other alkaline salts, never caused any distinct increase—indeed, in most of them there was apparently a lessening—in the secretion of the liver. Purgatives, including gamboge, jalap, convolvulin, rhubarb, aloes, podophyllin, calomel, etc., were equally without distinct effect. Diarrhoea of itself had no influence on the amount of bile. Atropine very distinctly, pilocarpine, alcohol and olive oil less distinctly, lessened the flow of bile. Antifebrin, antipyrine, caffeine, santonin, and oil of turpentine, had a feeble cholagogic action. The only substances which were found to possess any certain or powerful influence in increasing the flow of bile were the salicylates, bile itself, or bile salts.

These facts, determined in the lower animals, seem to hold true also for man. In a case of biliary fistula, Pfaff and Balch found that the biliary secretion varied extraordinarily and inexplicably; that it was apparently not affected either by calomel or corrosive sublimate; that salol increases the watery flow and the solids of the bile distinctly; but that oxgall had a very remarkable effect, increasing the amount of the bile as well as the percentage of its solid contents, the biliary acids being especially thrown off in extraordinary quantity. On the other hand, in a similar case, Wm. Bain reached the conclusion that Kissingen and Carlsbad water,



euonymin, sodium benzoate and sodium salicylate increased both the amount of bile and its solids while podophyllum resin increased the solid but not the fluid portion of the bile.

**Therapeutics.**—A mercurial purge is especially indicated by the congeries of symptoms known as *biliousness*: a heavily coated tongue, bitter, disagreeable taste, severe headache, depression of spirits, loss of appetite, slight nausea, and light-colored passages. It should be borne in mind that one or several of these symptoms may be absent in any individual case. Of all single indications for the use of calomel, the occurrence of *potter's-clay-colored* passages is the most important; and if such stools exist, and do not depend upon an organic cause, repeated small doses of the mercurial should be given, whether there be constipation or diarrhœa.

In *bilious fever*,—*i.e.*, malarial fever with congestion of the liver,—a mercurial purge, or several mild mercurial purges, will often, by exciting the action of the hepatic gland, be of great service in preparing the way for or aiding in the action of quinine. In *catarrhal jaundice*, mercurials, on the whole, offer, we think, the most frequently successful mode of treatment. It is evident that in such cases calomel does good not merely by its cholagogue influence, but even to a greater extent by its antiphlogistic power, no doubt lessening the viscosity of the secretions and abating the inflammatory action in the hepatic ducts. In many instances it is well to exhibit the mercurial in purgative doses to start with; but the main reliance is to be placed in the continuous exhibition of small doses of the drug until the gums are rendered slightly sore. Anything like profuse salivation is, of course, to be avoided. In *dysentery* of an acute sthenic type, calomel acts as an antiphlogistic and as an alterative, not only to the liver, but to all the intestinal glands. It is possible that it acts also as a bactericide, since N. P. Wassilieff has found that although it has no effect in checking the action of the digestive ferments, it has a very pronounced influence in stopping putrefactive changes in food by killing the organisms which produce such changes.

### RESINOUS CATHARTICS.

As already stated, most of the cathartics of this group are intensely irritant and belong to the old class of *drastic* purgatives; many of them are capable of causing fatal gastro-enteritis. Euonymus and leptandra are, however, comparatively mild in their action. The group is characterized by containing irritant resins for their active principles, these resins are usually glucosidal and more or less closely related to each other in chemical as well as physiological properties.\*

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\* Croton oil, which on account of its irritant properties is clinically related to this group, is considered under the head of cathartic oils.

**JALAP.**

The tuberous root of *Exogonium Purga*, a convolvulaceous vine growing in Mexico. Jalap comes into the market in two forms: one, that of the younger roots, which are sold undivided; the other, that of the old roots, which are brought into the market in transverse or longitudinal slices and in pieces. The first variety consists of very hard, irregularly globular, brittle roots, about the size of a fist, or smaller, and often slashed with vertical incisions, made for the purpose of facilitating drying. Jalap contains a resinous glucoside *convolvulin* and a smaller quantity of another resin which appears to be identical with *scammonin*. The Pharmacopœia requires that it contain not less than 7 per cent. of resin.

**Official Preparations :**

Jalapa .....	10 to 20 grains (0.6–1.3 Gm.).
Resina Jalapæ .....	2 to 4 grains (0.12–0.25 Gm.).
Pulvis Jalapæ Compositus (Jalap 35, Potas- sium Bitartrate 65) .....	$\frac{1}{2}$ to 1 drachm (2–4 Gm.).

**Physiological Action.**—Upon dogs and horses jalap (Stillé) is said to act as a powerful hydragogue cathartic, and in overdoses as a gastro-intestinal irritant. Its active principles are absorbed, since Cadet de Gassicourt produced diarrhœa in dogs by the free application of jalap to the shaven skin, and J. Müller found the resin in the blood of dogs to which he had given it. Stillé, however, asserts that it does not impart its purgative properties to the milk of nursing women, and that in man it is not absorbed by the skin. In man jalap produces free hydragogue catharsis, often with nausea; or, if in overdoses, violent vomiting and purging.

**Therapeutics.**—Jalap is especially indicated when it is desirable to produce large watery stools. It is, however, very rarely used alone. A favorite combination with many practitioners is of it and calomel. In the form of the compound powder jalap is very frequently used with great advantage in *ascites* and also in other forms of general *dropsy*. It is believed when given in this way to exert some influence upon the renal functions: for very many cases the proportion of potassium bitartrate in the official compound powder is too small.

**COLOCYNTH.**

The fruit, deprived of its rind, of *Citrullus Colocynthis*, or bitter cucumber, a vine growing in South Africa, Japan, Syria, Egypt, Turkey, the islands of the Grecian Archipelago, etc. The fruit is a round gourd, from two to four inches in diameter, of a whitish or pale yellow color. It occurs in the market with or without its rind. The pulp is dry and membranous, whitish, and contains the active purgative glucoside *colocynthin*, first discovered by Herberger.

**Official Preparations :**

Extractum Colocynthisidis.....	3 to 5 grains (0.2-0.3 Gm.).
Extractum Colocynthisidis Compositum (Ex- tract of Colocynth 16, Purified Aloes 50, Resin of Scammony 14, Cardamom 6, Soap 14).....	1 to 3 grains (0.06-0.2 Gm.).
Pilulæ Catharticiæ Compositæ (each pill contains Compound Extract of Colocynth 0.08 Gm., Calomel 0.06 Gm., Resin of Jalap 0.02 Gm., Gamboge 0.015 Gm.).....	1 to 3 pills.
Pilulæ Catharticiæ Vegetabiles (each pill con- tains Compound Extract of Colocynth 0.06 Gm., Resin of Jalap 0.02 Gm., Resin of Podophyllum 0.015 Gm., Extract of Lep- tandra 0.015 Gm., Extract of Hyoscyamus 0.03 Gm., Oil of Peppermint 0.015 Gm.)....	1 to 3 pills.

Colocynth in large dose is an irritant hydragogue cathartic, capable of destroying life, and, according to Orfila and Schroff, acting upon the lower animals as upon man. Christison records the death of a woman twenty-four hours after taking a teaspoonful and a half of the powder. Roques chronicles a fatal result produced by less than a drachm of the powder in decoction, but, on the other hand, narrates a case in which three drachms failed to kill (Husemann), and W. A. Rolfe reports recovery after a quarter of an ounce of the powdered drug in which, although pregnancy existed, abortion was not produced.

**Administration.**—It should not be used in *dropsy*, and is employed almost solely in combination with other purgatives.

**SCAMMONY.**

A resinous exudation from the root of *Convolvulus Scammonia*, a vine growing in Syria. It is said to be obtained by cutting off the root obliquely about two inches from the origin of the stems, and catching in shells the few drachms of milky juice which exude from each root. From these shells it is emptied into a vessel and allowed to concrete. It occurs in pieces of various sizes of a brownish-green color and a peculiar odor like that of old cheese. *Scammonin*, the active resin of scammony, is believed to be identical with *jalapin*, originally separated by Mayer from male jalap, and closely allied to *convolvulin* of true jalap. Therapeutically scammony acts like jalap, but is somewhat more irritating. It is almost solely used in combination with other cathartics, and on account of its frequent adulteration should be given in the form of the resin (*RESINA SCAMMONII*). Dose, from two to five grains (0.13-0.3 Gm.).

**PODOPHYLLUM.**

The rhizome of *Podophyllum peltatum*, or May-apple, a perennial herb, growing in the Northern and Middle United States. *Podophyllum* occurs in simple or branched, cylindrical, brownish pieces, about the thickness of a goose-quill, smooth or wrinkled longitudinally,



often obscurely marked with the scars of leaf-scales, and furnished with numerous rootlets or their remnants attached to the lower surface. The taste is bitterish, acrid, and nauseous. The rhizome contains the alkaloid *berberine*, but the purgative power resides chiefly in *podophyllotoxin*\* of Podwysotszki, although it is probable that there are other purgative substances in the rhizome, especially an uncrystallizable resin, *podophylloresin*.

Podophyllum is a rather slowly acting, but very thorough cathartic, whose large dose either in man or in most of the domestic animals produces violent purging, with great pain, and often with vomiting; the symptoms increasing, if the dose have been sufficient, to excessive hypercatharsis, with bloody stools, great prostration, and death. It is said to act when given hypodermically. A child four years old was killed by an unknown amount. The symptoms were repeated vomiting, slight purging, collapse, and finally coma, ending in epileptiform convulsions (T. G. Morton). An infant twenty-two months old recovered from four grains.†

#### Official Preparations :

Resina Podophylli. ....	$\frac{1}{2}$ to $\frac{1}{2}$ grain (0.005–0.01 Gm.).
Pilulæ Podophylli, Belladonnæ et Capsici	
(Each $\frac{1}{4}$ grain of Resin) .....	1 pill.
Fluidextractum Podophylli. ....	8 minims (0.5 C.c.).

In therapeutic doses it is believed by very many practitioners to act especially upon the liver, and is much used in acute *constipation* and in so-called *bilious attacks*. As ten or more hours are usually required for its action, it should not be combined with quick cathartics. With calomel it acts very well. The only preparation that should be used is the resin or *podophyllin*.

#### ELATERIUM.

A substance deposited by the juice of the fruit of *Ecballium Elaterium*, or squirting cucumber, a native of Greece, but cultivated in England. In the interior of the ovate fruit is an elastic sac, which contains the seeds, and at ripening becomes so distended with juice that when the fruit falls off the vine, and the support is removed from the stem end, a rupture occurs at the latter position, and the liquid with the seeds is forcibly projected. The medicinal principle is said to be contained only in this inner juice. In order to avoid loss, the fruit is picked with a piece of the stalk adherent to it before ripening, and is opened by slicing. *Elaterium* occurs in light, friable, slightly incurved, greenish-gray cakes about a line thick. The taste is acrid and bitter, the fracture finely granular. Owing to the variability

\* Podophyllotoxin was believed by its discoverer to be composed of *picropodophyllin* in combination with *podophyllinic acid*. Later chemical researches indicate, however, that these substances are decomposition products. Podophyllotoxin appears to be a very irritant, active cathartic, and has been used in medicine in doses of one-fifteenth of a grain. According to J. Neuberger (*Arch. f. Exper. Path. u. Pharm.*, 1890, xxviii.), it causes in the lower animals violent purging and severe nephritis, with fall of the arterial pressure and death from exhaustion.

† *Australasian Med. Gaz.*, ii. 237.

of commercial elaterium, the U. S. Pharmacopœia now recognizes only the active principle, *Elaterin*, which was first separated in a pure state by Morris. It crystallizes in colorless, shining, rhombic, six-sided, odorless tables, of a very bitter sharp taste and neutral reaction.

#### Official Preparations:

Elaterinum..... $\frac{1}{30}$  to  $\frac{1}{12}$  grain (3-5 Milligm.).  
Trituratio Elaterini (10 per cent.)..... $\frac{1}{2}$  grain (0.03 Gm.).

**Physiological Action.**—Locally applied, elaterium is a very decided irritant, producing, according to Pereira, ulcerations in the fingers of those who handle the fruit and prepare the drug for market. When taken internally, it acts on man as a most powerful hydragogue cathartic.

Kohler has proved that in animals elaterium is absorbed, even when given by the mouth, since he found it in the urine of poisoned dogs and rabbits.

**Therapeutics.**—Elaterium is certainly the most efficient of all the hydragogue cathartics, producing in properly regulated doses the freest evacuations with comparatively little pain and irritation and is much used in the treatment of general *dropsy* or *ascites*. As, however, its action is very exhausting, great care should be exercised not to give it in too large doses, and also to support the strength of the patient during the period of purgation, and afterwards, by alcoholic stimulants, easily digested nutritious food, and appropriate hygienic measures. In the latter stages of dropsy the injudicious use of elaterium may cause a fatal exhaustion. For the asserted power of elaterium in increasing the intestinal elimination of urea we have been unable to find authority. Clinical experience has, however, demonstrated the value of elaterium in *uremia*. In order to deplete, elaterium has been employed in various diseases; but this use is not to be encouraged, and especially when there is any gastro-intestinal irritation or inflammation are the salines much preferable to elaterium.

Elaterium is without doubt capable of destroying life, but we know of but one recorded death,—that of a woman in whom two and two-fifths grains of the extract of elaterium and sixteen grains of rhubarb caused uncontrollable vomiting and purging, ending in a fatal gastro-enteritis.\*

#### GAMBOGE.

A gum resin, obtained in Siam by breaking off the leaves and young shoots of the tree known as *Garcinia Hanburii* and catching in suitable vessels the juice as it drops. When the receptacles consist of hollow bamboos, the juice hardens into cylindrical casts, striated externally, and with a central cavity due to the loss of substance in

\* See *Beck's Medical Jurisprudence*, 12th ed., ii. 719.

drying. This is the so-called *pipe gamboge*. *Gamboge in sorts* occurs in irregular masses. Gamboge is a hard, resinoid substance, of a brittle, often conchoidal fracture, of a deep reddish-orange color on exposed surfaces, more yellowish when freshly broken, affording a bright yellow powder, insoluble in water, with which it forms, however, a bright yellow emulsion. It has little or no taste, but when chewed produces, after a time, an acrid sensation in the fauces.

**Physiological Action.**—Gamboge acts upon man as a violently irritant cathartic. On the lower animals it has a similar influence, but Schaur and Orfila state that when in large dose it often fails to purge, producing rapidly fatal gastro-enteritis, so intense as seemingly to paralyze the bowels. According to Daraszkievicz and to Schaur, in order for gambogic acid to act as a purgative the presence of bile in the intestine is necessary. Schaur and Richter affirm that gamboge upon raw surfaces acts simply as an irritant: further, Gmelin and Tiedemann assert that they have found its principles in the urine; it may therefore well be that solution by the alkaline fluids of the intestines is necessary for its purgative action. Lewis, Abeille, and Ferriar state that, when given in certain ways, gamboge acts as a decided diuretic. If this be true, absorption of its active principle must occur. Schaur was not able, however, to detect it in the urine of persons or of animals taking it. Even when he injected large quantities of it into the blood of dogs he failed to find it in the urine, although he did obtain a resinoid substance which he believes to be a derivative.

Gamboge is so irritant that it is used in practical medicine only to give sharpness to purgative combinations. The full purgative dose would be from two to five grains (0.13–0.3 Gm.).

**EUONYMUS**, or *Wahoo*, the bark of *Euonymus atropurpureus*, contains a glucosidal resin, *euonymin*, which is stated to have a digitalis-like action on the heart. Wahoo was found by Noel Paton, when given to dogs in small dose, to increase greatly the elimination of urea and uric acid, and by Rutherford to be in large dose an active cholagogue in dogs. In man its effects are often most happy in cases of *habitual constipation* and *hepatic torpor*. It acts very slowly and purges only moderately. The dose of the extract (**FLUIDEXTRACTUM EUONYMI**) is eight minims (0.5 C.c.); of its extract (**EXTRACTUM EUONYMI**) (the best preparation), two to four grains (0.13–0.26 Gm.); in cases of *dyspepsia* it may be repeated with good results two or three times a week.

**LEPTANDRA**.—The rhizome and roots of *Veronica virginica*, when given in a fresh state, are apparently cathartic, but in their officinal dried form are mild and less certain. The active principle seems to be the glucoside *leptandrin*. Leptandra is believed by various practitioners to have special cholagogue properties, and in Rutherford's experiments upon dogs the impure resin acted feebly upon the liver. The U. S. Pharmacopœia recognizes the fluidextract (**FLUIDEXTRACTUM LEPTANDRI**). Dose, one-half to one fluidrachm.

## CATHARTIC OILS.

Ordinary oleic acid has a mildly laxative effect and for this reason olive oil and soap are occasionally employed in the lighter forms of constipation. The closely allied bodies, however, known as croton-



oleic acid and ricinoleic acid are actively purgative. Apparently the oils themselves, *i.e.*, the glycerides of these acids, are not cathartic, only the free acid being active. In the case of croton oil there is present with the oil a certain amount of free crotonoleic acid, the drug, therefore, acts quickly and also exercises its irritant action upon the stomach. In the case of castor oil, however, the free acid is not naturally found and the remedy becomes active only after saponification which takes place in the intestinal tract; therefore it acts more slowly and has no irritant effect upon the stomach.

### CASTOR OIL.

A fixed, nearly odorless oil, of a nauseous taste, obtained from the seeds of *Ricinus communis*, a shrub native to India, by expression. The seeds are slightly warmed before being put under pressure, so as to liquefy their contained oil; and the crude oil obtained from them is boiled with a small amount of water, so as to coagulate its albuminous impurities. Castor oil is remarkable for being soluble not only in ether, but also in alcohol. The *castor-oil seeds*, or *beans*, as they are commonly called, contain an acrid, violently poisonous principle, *ricin*.\*

**Physiological Action.**—Castor oil acts upon the human organism as a mild but decided purgative, producing copious fluid fecal discharges, and in overdoses sometimes vomiting, and always purging freely. The bulk of the castor oil is *ricinolein*, a glyceride of *ricinoleic acid*, which appears to be the purgative principle, and to be absorbed; at least Canvane† affirms that in children castor oil sometimes purges when rubbed upon the skin of the abdomen, and when taken into the stomach it has been known to exude from the skin.‡ Buchheim, although he submitted the passages produced by the oil to careful chemical manipulation, failed to detect it or any derivatives. According to the experiment (quoted by Stillé) of Hale upon himself, half an ounce of castor oil injected into a vein produces malaise, nausea, faintness, anxiety, and general dulness and depression, without purging.

**Therapeutics.**—On account of the mildness of its action and a special property of soothing an irritated bowel, castor oil is constantly employed whenever it is desired simply to evacuate the intestinal canal; not so much, however, in *chronic constipation* as when a temporary action is alone required. In various inflammatory or irritative affections of the alimentary canal, castor oil is often of the greatest service. This is especially seen in the acute *diarrhæas* and

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\* Three beans have caused death in the adult. The symptoms, which do not usually come on until from two to five hours, are severe abdominal pain, violent vomiting and purging, which after a time may become bloody, collapse, severe muscular cramps, cold sweating skin, contracted features, thirst, restlessness, and small rapid pulse. After death, intense redness and even abrasion of the stomach and of the small intestine are found. After the stomach and large intestine have been thoroughly washed out with warm water, the treatment of castor bean poisoning is that of toxic gastro-enteritis,—namely, the use of opium, leeches, ice, demulcent drinks, counter-irritation, etc. See Kobert and Stillmark (*Arbeiten Pharmak. Inst. zu Dorpat*, iii.).

† See H. Meyer (*Arch. f. Exper. Pathol. u. Pharm.*, 1890, xxviii.).

‡ Ward's case (*London Med. Gaz.*, x. 377).

even in the *chronic enteritis* of children, but also holds good in the *diarrhæas* and *dysenteries* of adults. In *chronic pseudo-membranous colitis* we have seen very excellent results from the long-continued daily use of the oil.

### CROTON OIL.

The fixed oil obtained from the seeds of *Croton Tiglium*, a euphorbiaceous shrub of Hindostan and other portions of Southern Asia. This oil is quite viscid, varies in color from a pale yellow to a dark reddish brown, and has an acid reaction. Its taste is hot, acrid, and extremely persistent; its odor faint, but peculiar. Croton oil consists chiefly of the glycerides of ordinary fatty acids, but contains also *crotonoleic acid*, which has been supposed to be its pure active principle, but is stated by Dunstan and Boole to be a mixture of inactive oily acids with a powerfully vesicating, resinous substance, *croton-resin*.

**Therapeutics.**—Locally applied, croton oil is an intense irritant, producing upon the skin an eruption which is at first papular but in a very short time becomes pustular.\* (See COUNTER-IRRITANTS.) Administered internally, croton oil produces in man and in most of the lower animals violent purging, with severe griping, and is capable of causing a fatal gastro-enteritis. Its action on the intestine is probably in part local and in part through absorption. In the experiments of Hertwig (quoted by Stillé) and of Buchheim, purgation did not follow the injection of the oil into the veins of animals; but Conwell obtained a result contrary to this, and there is considerable testimony that its external use in man is sometimes followed by purging (Stillé), and even by fatal results.† The experiments of Kobert and of Hirschheydt seem to prove that crotonoleic acid is both the purgative and vesicant active principle: it exists in the oil combined with glycerin. It is believed that the glyceride is slowly decomposed in the intestines, and that the acid which is thus set free acts progressively. Certainly, Hirschheydt found that pure crotonoleic acid, which has appeared in commerce, is not a practical purgative, ten milligrammes being very uncertain in their effects, while large doses are prone to produce excessive gastro-intestinal irritation. Injected into the blood, crotonoleic acid was found to be an exceedingly active depressant to the circulation. The amount of free crotonoleic acid in croton oil increases very markedly with age. On this account old croton oil, with an acid reaction, acts much more harshly than does the recent neutral or nearly neutral oil, and should be rejected for internal use.

**Therapeutics.**—Croton oil is chiefly used in practical medicine in *mania*, *apoplexy*, or other diseases in which there is difficulty in administering a cathartic. It is also given in cases of very obstinate constipation when less active remedies have failed. It is the one cathartic employed when, as in some brain diseases, it is desired to

\* For a histological study of the eruption, see *Wiener Med. Wochenschr.*, 1897, xlvii, 1021.

† See *Schmidt's Jahrb.*, clxiv.; also *Kobert's Arbeiten*, 1890, iv, 45.

revulse by the intestines. The dose is one drop, in emulsion, or by simply placing it upon the tongue. In overdoses, croton oil is a violent poison.

**Toxicology.**—Although in small amounts croton oil causes such severe symptoms, yet in larger quantities it has failed to produce as serious results as would be naturally expected. It is, however, very possible that in at least some of the recorded cases the oil was adulterated. Cowan has reported a case (Husemann) of a child four years old who recovered in two days from a teaspoonful of croton oil taken on a full stomach; Adams (Husemann) saw recovery in an adult after the ingestion of a drachm; and the case is recorded of a woman who took about an ounce, was vomited forty-five minutes afterwards with mustard, and finally recovered. The minimum fatal dose is not known, and probably varies greatly. A child aged thirteen months was killed by a quantity believed not to exceed three minims. Giacomini (Stillé) reports a case in which twenty-four grains of the drug proved fatal in as many hours: although there were but four stools, the patient presented the symptoms of general collapse, preserving consciousness to the last. A little less than two drachms has caused vomiting and death without purging.\*

The treatment of croton-oil poisoning is purely symptomatic. Opium should be given to lessen the purging, demulcent drinks to lessen the irritation. If collapse develops, cardiac stimulants should be administered hypodermically and bodily temperature maintained by the application of external heat.

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## FAMILY IV.—DIURETICS.

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While, strictly speaking, the term diuretics refers to those drugs which increase the flow of urine, in this chapter are included not only these but also drugs which are used for the purpose of affecting the mucous membrane of the urinary tract.

**Effect of Water.**—The quantity of urine excreted depends to a great extent upon the volume of the blood. Any agency, therefore, which tends to make the blood more voluminous increases the quantity of urine, and, on the other hand, those influences which make the blood more concentrated diminish it. For this reason when other glands of the body are abnormally active, especially the bowel and skin, because of the excess of fluids escaping through these channels, the quantity of urine is diminished, and *vice versa*, a diminution in the activity of the sweat glands tends to the production of diuresis. Cooling of the surface, therefore, by checking the skin secretions, increases the quantity of urine. These facts must be borne in mind in using diuretics. Certain drugs, for example pilocarpine, may be made to act either as diaphoretics or as diuretics by alterations of the temperature of the patient's surroundings.

Of still greater importance is the introduction of water into the system either by having the patient drink freely, or by the injection of physiological salt solution. Either of these measures in a healthy organism leads to a marked increase in the quantity of the urine excreted.

A matter of great importance in this connection is the effect of the ingestion of water upon the elimination of the solid constituents through the urine. Although some of the older investigators, notably Böcker, failed to obtain any increase in the total amount of nitrogenous material eliminated through the use of water, the preponderance of testimony is so strong that it must be considered as proven that, in ordinary conditions, not only the total bulk of urine but also the quantity of solid matter is increased by the administration of water. Whether this increase of urinary solids betokens a more active metabolism, or whether it merely indicates a washing out of already formed waste products, cannot be so definitely answered. Meyer, Voit, and many others maintain that the increase in solids is simply the result of flushing the system and that, if the administration of water is continued, the primary augmentation of solid matter gives way to a marked decrease in the urinary nitrogen after the accumulated products of metabolism have been flushed out. On the other hand, the experiments of Landauer, and of Edsall, and others, indicate

strongly that, while the solid matter eliminated is largely stored up waste products, there is also a distinct, if slight, increase in the destruction of proteid tissues.

It is evident, from the above, that water may become a valuable remedy in the treatment of many conditions of the urinary tract. In the first place, frequently it is useful for the purpose of getting rid of accumulated metabolic poisons. Thus it is sometimes of service in the treatment of *uremia*, especially in the more acute types. It has, however, a still larger field for usefulness in the excretion of the metabolic poisons giving rise to those symptoms commonly spoken of as lithemic,—as *gout*, *chronic rheumatism*, and the like.

Again, in cases of *suppression of the urine*, whether due to the effects of irritant poisons or hemorrhage, the administration of fluids is frequently of great service in re-establishing the urinary activity. In the first case by diluting the blood and hence lessening the concentration of the solution of the irritant, it decreases the irritation of the kidney. In the latter case it leads to a filling of the vessels which have been emptied by the loss of blood and offers, again, fluid for the kidney to excrete. Frequently, also, it is of service to prevent irritation of the kidney, as in lithemia, by rendering the urine more dilute. In the same way it may be used to make the excretions more bland in cases of *irritation of the bladder*.

For medicinal purposes, water may be introduced into the system through one of three channels; the alimentary tract, subcutaneous tissue, or intravenous injection. In chronic cases, where the immediate effect is not a matter of great moment, for obvious reasons it is generally preferable to simply have the patient drink regularly large quantities of fluid. Where, however, the condition is more serious the fluid may be introduced by *hypodermoclysis*. For this purpose we believe an 0.9-per-cent. solution of sodium chloride is the best. This should be warmed to a temperature of about 102° F. and injected slowly into the subcutaneous tissue, either of the thorax, abdomen, or back. A fountain syringe placed about three feet above the patient ordinarily affords sufficient power, and, if the injection is carried out carefully, from one-half to one pint of solution may be injected in one part without much discomfort. If it is desirable to introduce larger quantities the needle should be withdrawn and introduced into another portion of the body. Needless to say the operation should be done with strictest aseptic precautions. In conditions of great immediate danger it is sometimes necessary to inject the fluid directly into the vein.

The subcutaneous or intravenous injection of physiological salt solution is very largely used in the treatment of conditions not directly associated with kidney function. In cases of circulatory failure or *collapse* due to the loss of blood or surgical *shock* it is a measure of great service, for the purpose of maintaining the activity of the heart. As a circulatory stimulant in cases of essential heart failure, dependent, for example, upon cardiac dilatation, or in the presence of cardiac



depressant poisons, the value of the treatment is far less certain. It has also been recommended, by Delbert and others, in the treatment of various forms of poisoning with the idea that it will hasten the elimination of the poison. While Delbert has shown that with the free intravenous injection of salt solution suprafatal doses of strychnine are borne by the dog without the development of poisoning, it is probable that the fluid acts by diluting the concentration of the poison in the blood, rather than by increasing its elimination.

The chief indications for the use of diuretics are as follows:

1. *To maintain the action of the kidneys.* It is hardly necessary here to discuss the necessity of excretion to the system. In various kidney diseases this indication is very urgent; but as the lessened excretion too often depends upon a profound organic alteration of the renal secreting structure, it is evident that very frequently diuretics must fail when most needed. In the great majority of cases in which diuretics are used to fulfil the present indication, only the mildest of the class should be employed. Whenever there is inflammation of the kidneys, even if it be chronic, irritating diuretics should be avoided. When lessened urinary excretion is purely functional in its origin, diuretics are often most serviceable. In fevers especially is it necessary to maintain the action of the kidneys; for this purpose water should always be freely given during fever. The alkaline diuretics sometimes may be exhibited; but the most generally serviceable of all remedies of the class in the febrile state is the sweet spirit of nitre.

2. *To evacuate fluid.* For this purpose hydragogue diuretics are employed in all forms of dropsy.

3. *To soothe and diminish irritation of the genito-urinary organs.* The value of water in fulfilling this and the next indication has already been pointed out. By lessening the acidity of the urine and rendering soluble the uric acid which is present, the alkalies are equally important in carrying out the present and the following indication.

4. *To alter the urinary secretion so as to prevent the deposition of calculous material.* Notwithstanding it has been otherwise asserted, no practical measure has as yet been devised of dissolving a calculus when once formed. Even to alter the urine so as to prevent further deposition is probably impracticable, except in cases of uric acid or phosphatic diathesis.

The diuretics may be divided into three groups: 1, Those that affect the kidney indirectly by increasing the amount of blood which passes through it, in other words the circulatory stimulants; 2, those which have a direct irritant or stimulant action upon the kidney cells—Stimulating Diuretics; 3, substances which change the osmotic relations of the blood—Saline Diuretics. There are also included in this chapter certain drugs which are used not so much for their effects in increasing the quantity of the urine but for their local action upon the mucous membrane of the urinary tract—Alterative Diuretics.

## STIMULATING DIURETICS.

Of the drugs belonging to this group *strophanthus*, *apocynum*, and *caffeine* are considered in the chapter on Cardiac Stimulants. Any locally irritant substance which passes out through the kidney may, by its irritant influence, increase the flow of urine. Certain drugs of this character, notably oil of juniper, have been used to a considerable extent as stimulating diuretics, but, on account of their other properties, are considered elsewhere.

## SQUILL.

The bulb of *Urginea maritima*, a liliaceous plant growing in the south of Europe, especially on the shores of the Mediterranean. The bulb varies in size from that of a child's head to that of the fist. It is composed of numerous layers or scales, which separate when it is sliced for drying. As kept in the shops, squill is in horny flakes, of a white or red color, becoming leathery when wet, and having an acrid, bitter taste. It yields to water and alcohol and also to vinegar.

The nature of the active principle of squill has not been established. A number of glucosides have been described by chemists, and Merck has put upon the market three substances, *scillin*, *scillipicrin*, and *scillitoxin*.\* There is, however, no sufficient proof as to which, if any, of these substances represents the crude drug.

## Official Preparations :

Scilla.....	1 to 3 grains (0.06–0.2 Gm.).
Fluidextractum Scillæ.....	1 to 3 minims (0.06–0.2 C.c.).
Tinctura Scillæ (10 per cent.).....	10 to 20 minims (0.6–1.2 C.c.).
Acetum Scillæ (10 per cent.).....	10 to 20 minims (0.6–1.2 C.c.).
Syrupus Scillæ (4½ per cent.).....	½ to 1 fluidrachm (2–4 C.c.).
Syrupus Scillæ Compositus (Squill and Senega each 8 per cent., tartar emetic $\frac{1}{16}$ per cent.) [Coxe's Hive Syrup].....	1 fluidrachm (4 C.c.).

**Physiological Action.**—*Kidney*.—Squill is a stimulant to the kidneys, and in overdoses causes an irritation whose result is lessening of the secretion, scanty bloody urine, or absolute suppression of urine, according to the amount of the poison ingested. Its diuretic action has been noted in animals by Schroff and by Chiarenti (quoted by Stillé), and there can be no doubt as to the power that squill has of increasing the watery portion of the urine. We know of no studies upon its action on the urinary solids. According to Stillé, the external application of squill will produce its characteristic effects on the system.

\* Frommüller has reported (*Memorabilien*, 1879, xxiv. 250) a series of experiments made, upon persons suffering from various ailments, with the scillin, scillipicrin, and scillitoxin of Merck. He found that scillitoxin in doses of 0.45 grain acted as a rather uncertain diuretic, and frequently caused giddiness, headache, and loss of appetite; scillin seemed to be devoid of diuretic properties; while a gramme of a solution of scillipicrin in water (one part in fifty) administered hypodermically usually caused a great flow of urine, without other evil symptoms than some smarting at the place of injection.

**Circulation.**—It is certain that squill contains some substance which acts similarly to digitalis on the heart, and that this is to be found in the extract.

C. Lupinski found that scillitoxin is a powerful stimulant to the peripheral vagi in the frog, causing slowing of the pulse, and in certain doses diastolic cardiac arrest, and in the dog slowing of the heart. Large doses cause in the frog tetanic contractions of the heart. He also found that in the dog large doses finally paralyze the peripheral vagi and produce a rapid pulse. The arterial pressure is increased, partly, it is affirmed, by the increased cardiac energy, and partly by a peripherally produced vaso-motor contraction.

Husemann affirms that the extract has no expectorant properties; that it is a digitalis-like, cardiac stimulant, and acts as a diuretic solely by affecting the renal circulation.

**Therapeutics.**—Squill is a valuable remedy in *dropsy* when the condition of the system is atonic and when there is no disease of the kidney. It may even be used with advantage in *serous effusion* into the *pleura* or the *pericardium* dependent upon chronic inflammation of the membrane, especially in combination with calomel. A pill of one grain (0.06 Gm.) each of squill and digitalis is very efficient in *cardiac dropsy*; sometimes the addition of calomel is advantageous. The one contraindication to the use of squill is the existence of Bright's disease or of acute irritation of the kidney.

**Toxicology.**—In poisonous doses squills causes great abdominal pain, violent purging and vomiting, lessened or almost suppressed secretion of bloody albuminous urine, with slow pulse, ending, it may be, in collapse, convulsions, and death. According to Husemann, twenty-four grains of squill have caused death.

The treatment of the poisoning consists in the evacuation of the stomach and bowels by ipecacuanha and castor oil, if nature has not already fulfilled the indication; the free use of opium; the exhibition of large quantities of water, for its action on the kidneys; and the usual measures for the relief of gastro-enteritis, if much tenderness be present. Early in the poisoning care should be exercised in the exhibition of alcoholic stimulants, for fear of increasing the gastric irritation; during the stage of collapse they may be imperatively demanded, and with their use should be combined that of dry heat applied externally, and of the other usual measures of relief during collapse.

**Administration.**—As a diuretic, squill should be given in solid form, one or two grains (0.06–0.12 Gm.) every three hours, the dose being gradually increased until some nausea is felt.

### SCOPARIUS.

Scoparius is the dry tops of *Cytisus Scoparius*, or the common broom-plant of Europe, which is cultivated in this country and has in some places escaped from the gardens. It occurs as greenish twigs, with minute downy leaves, has a bitter, nauseous taste, and, when bruised, a peculiar odor, and yields its virtues to hot water.



Stenhouse discovered in *scoparius* a neutralized crystallizable principle, *Scoparin*, which probably represents the purgative and diuretic influences of the drug, and also a liquid alkaloid, *Sparteine*. (See *sparteine sulphate*, page 248.

In overdoses, *scoparius* causes free purging, and even vomiting; but as ordinarily administered it is an efficient hydragogue diuretic, which is much used in general *dropsy*, and is one of the most reliable remedies of its class. It is best given in decoction,—half an ounce of the tops in a pint of water boiled down to half a pint; of this an ounce may be given every three hours until some effect is produced; or a fluidextract, which is not official, may be given in half-drachm (2.0 C.c.) doses.

MERCURY.—Many years ago therapeutic writers, notably George B. Wood, asserted that the combination of digitalis, squill, and calomel yields in the treatment of dropsy, and especially of cardiac dropsy, diuretic results much superior to either of the vegetable products alone; but more recently E. Jendrassik directed attention to the great practical value of calomel as a diuretic.

The present experimental evidence in regard to the effect of mercury upon diuresis in the lower animals is contradictory. W. Cohnstein affirms that the hypodermic injection of the mercurial produces very quick active diuresis in the rabbit, but Vejun-Tyrode and Nelson failed to get a consistent diuretic action either in the dog, cat, or in the rabbit; as they affirm that "throughout all these experiments there were evidences of more or less severe renal irritation as shown by the presence of blood and casts and by diuresis," it is probable that they employed the calomel in too large doses.

According to Brasse and Wirth, when mercury is given hypodermically in large dose it soon appears in the urine, which is markedly increased in quantity; if, as not rarely happens, the urine becomes albuminous, excretion of mercury at once ceases, albumin and mercury never coexisting in the urine. Silva, experimenting with defibrinated blood, finds that the addition of a mercuric salt causes the kidney vessels to dilate, the local blood-pressure to rise, and secretion to increase. Moreover, it is certain that mercurials in excess cause desquamative nephritis; so that it must be concluded that these preparations either stimulate or irritate the renal secretory structure proportionately to the amount present. According to Bieganski, the diuretic effect is most active after subcutaneous injections and least so after inunctions.

The destruction of renal secreting tissue by disease without doubt interferes with the diuretic action of mercurials, but the fact remains that in chronic *parenchymatous nephritis* with alarming decrease in the secretion of urine, calomel is one of the most effective diuretics known. In *cardiac dropsy* it is often very efficient in improving not only the dropsy itself but the condition of the digestive organs. In some cases of chronic cardiac disease the continued use of minute doses of the mercurial is very advantageous, but when it is desired powerfully to affect the kidneys large doses of the drug are required. Under these circumstances, we have found the administration of five grains (0.3 Gm.) of calomel every two hours until fifteen grains (1 Gm.) in all are taken to act most happily. It is sometimes, though rarely,

necessary to use opium to check the purgative action of the calomel. When there is excessive debility some caution may be necessary in this use of mercurials, but we have seen life apparently saved for the time being by the removal of an acute *suppression of urine* in advanced *Bright's disease*.

### XANTHIN COMPOUNDS.

Xanthin, or Dioxypurin, yields the following compounds which are interesting therapeutically:

*First, Trimethylxanthin* or *Caffeine*, which we have already fully considered. (See p. 209.)

*Second, three isomeric dimethylxanthins:*

- 1.—Dimethylxanthin, Theobromine;
- 2.—Dimethylxanthin, Theophyllin (Theocin);
- 3.—Dimethylxanthin, Paraxanthin.

*Dimethylxanthin* or *Theobromine* has been chiefly used in the form of the *sodium theobromine salicylate*, a white powder, soluble in less than half its weight of warm water, and containing about forty-nine per cent. of theobromine. It has been put upon the market as a proprietary remedy under the name of *Diuretin*, which, according to analysis, contains from thirty to forty per cent. of theobromine. Attention was first called to theobromine as a practical remedy, in 1890, by C. Gram and Kouindig-Pomerantz.

**Physiological Action.**—Theobromine is rapidly absorbed, and has been shown by the studies of Albanese, Bondzynski and Gottlieb, and of Krüger and Schmidt, to be eliminated in part unchanged, and in part in the form of methylxanthin.\*

**General Effects.**—The ordinary dose of theobromine causes no distinct symptoms in man, and we know of no recorded cases of poisoning by it. According to I. M. Sabashnikoff large doses produce in the lower animals a quickening of the respiration, which is followed after a toxic dose by intense dyspnœa, high temperature, free salivation, vomiting, diarrhœa, and excessive diuresis. The elevation of temperature, which sometimes amounts to 4° C., is, according to Sabashnikoff, prevented by previous high section of the spinal cord.

The detailed physiological action of the drug has not been worked out; according to Sabashnikoff there is increased irritability of the motor area of the cerebral cortex, and upon the striated muscles the drug acts as does caffeine. The toxic dose lowers the arterial pressure. (Cohnstein and Bock.) Cohnstein found that the full therapeutic doses had no perceptible influence upon the blood-pressure, and in Bock's researches the pressure was only elevated occasionally, the most marked phenomenon being great increase in the

\* The researches mentioned show that the exact form of elimination, as well as the percentage of the various educts, varies in different species of animals, and very probably in different individuals under varying circumstances. In man, 3-methylxanthin seems to be the chief educt, though 7-methylxanthin (Heteroxanthin) has been found; while in rabbits 7-methylxanthin is especially produced.

frequency of the pulse-rate, probably due to excitation of the accelerator mechanism of the heart, since the vagi was found to be thoroughly active. As the result of studies made upon the isolated heart of the mammal, Bock believes the fall of pressure is due to an action upon the cardiac muscles, which decreases its elasticity. He also believes that the rise of pressure, sometimes produced by the small doses, is the result of the increased pulse frequency.

*Kidney.*—In the oncometrical studies of Gottlieb and Magnus, the increased diuresis was accompanied by an increase of the size of the kidney. In the chloralized animal these investigators found that the increased diuresis persisted, although the kidney was markedly below its normal size,—evidence that the diuresis is the outcome of a direct action upon the secretive power of the kidney.

**Therapeutics.**—Theobromine has been much used as a diuretic which is not irritant to the kidneys, and rarely causes disagreeable symptoms. It has been given in acute and chronic *nephritis* with excellent results, and has been especially recommended in *cardiac dropsy*, with the statement that it increases the force and regulates the character of the cardiac beat when the heart is weak. (See Masius, also Pawinski.) In rare cases it acts unfavorably, causing headaches, irregularity of the pulse, vomiting, diarrhoea, and even—according to W. Schmieden—hematuria. From eighty to one hundred and twenty grains (6–8 Gm.) may be administered during the course of the day, in capsules or solution, or hypodermically. According to Demme, to a child six years old twenty to thirty grains (1.2–2 Gm.) may be given in the twenty-four hours.

AGURIN is a white, slightly bitter powder, freely soluble in water, which is said to consist of five parts of theobromine acetate and two parts of sodium acetate. It should always be prescribed in the form of the powder, its solution not being stable, but should be taken in dilute solution in doses of ten to fifteen grains (0.6–1.0 Gm.) three or four times a day. In Mosauer's experiments agurin seemed to be more irritant to the kidneys than theobromine.

PARAXANTHIN. We have not much information concerning this substance, but, according to Dreser-Elberfeld, it acts in a manner similar to theocin, increasing the output of urinary solids as much as does that drug, but not having nearly as powerful an influence in the excretion of water from the kidneys.

THEOPHYLLIN or *Theocin* was first isolated from the tea-leaf by Kossel, but in such minute quantities as not to be a commercial product until the discovery by Traube that it could be produced by synthesis resulted in its being put upon the market under the name of *theocin*. It is a crystalline substance, soluble in one hundred and seventy-nine parts of water at 18° C., in eighty-five parts at 37° C. It was first brought forward by Minkowski, as a very active diuretic, and has been reported upon by a number of German clinicians. According to C. Doering, it is about as poisonous as caffeine, but Doering, Thienger, and Kramer all agree that it is much more active as a diuretic than is either caffeine or theobromine, increasing remarkably both the excretion of water and solid matters from the kidney. It has been tried both in *cardiac* and *renal dropsies* and is found to be very positive in its influence. Not rarely theocin has produced disagreeable symptoms, the most common of which are those of gastric irritation; in some cases severe vomiting, headache, and general malaise have been reported; and Schlesinger in two



cases noted the occurrence of epileptiform convulsions after the taking of five doses of 0.2 gramme of theocin. The effect of theocin is also likely to be temporary, the system apparently in a short time becoming accustomed to its use, so that it fails to cause diuresis.\* Its maximum effect is commonly apparent the second or third day of its ingestion. In order to avoid gastric irritation, it is better to give in frequent small doses up to 8 grains a day (0.5 Gm.).

### SALINE DIURETICS.

Under this class are included those substances which increase the flow of urine by altering the composition of the blood rather than by acting on the kidney itself. The present idea of their mode of action can be clearly comprehended only by some conception of the modern theory of the actions of salts and their ions.

**The Theory of Ions.**—A neutral salt is a body resulting from the union of an electro-positive and an electro-negative element or radical. According to the ionic theory, when a salt is dissolved in water it exists in the solution not merely as a solution of the neutral body but is broken up at least in part, into its electro-positive and electro-negative components. This dissociation, as it is called, is not the same as the chemical separation of the molecule into its constituent elements, for the solution does not have the properties that a solution of these elements should have; thus, in a dilute solution of sodium chloride we have the positive ion sodium and the negative ion chlorine, but the solution does not show any chemical signs of the presence of free chlorine. The evidence for the occurrence of this dissociation is based upon the physical properties of the solutions of the salts; for instance, the boiling point of a saline solution is increased proportionately to the number of molecules dissolved in the solution, but we find that frequently the increase in the boiling point is disproportionately too great to be explained by the amount of salt dissolved, hence it is believed that the salt exists not only as a salt but also as its component ions, each of which acts as a molecule.

Many bodies do not ionize at all; thus alcohol,  $C_2H_5OH$ , does not act as a hydroxyl of ethyl, but acts as alcohol. Generally speaking radicals do not split into their component elements, but the radical itself exists as a distinct ion; for instance, sodium sulphate,  $Na_2SO_4$ , dissociates into two sodium ions and one  $SO_4$  ion. Again, in the case of potassium ferrocyanide,  $K_4Fe(CN)_6$ , the ferrocyanide ion  $Fe(CN)_6$  remains intact, and the poisonous action of the cyanides is not developed.

Salts generally do not completely ionize, so that the amount of dissociation which occurs will depend upon the character of the salt and the concentration of the solution; generally speaking the more dilute the solution, the greater is the dissociation. Therefore in considering the effects which will be produced by the introduction

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\* Albanese believes that the rapid diminution of diuresis after the administration of theocin is due to the deposit in the renal canaliculi of crystals of trimethylxanthin; basing his belief upon microscopic studies, and upon the fact that he was enabled, by injecting large quantities of saline solution in the lower animals, to maintain the activity of the drug.

of a salt into the blood, we have to consider the action of the positive ion, of the negative ion, and of the salt itself; all of these factors are mutually concerned in what is known as the "salt action." There are certain properties and certain effects upon the system which are common to all crystallizable substances and are spoken of as "salt action." These effects are, to a large extent, connected with their influence on osmosis.

In the case of many salts one of the other ions may be so toxic as to completely overwhelm the action of the other ion as well as the salt action, thus after the administration of strychnine nitrate, no effect can be perceived except the effect of the strychnine ion; and with potassium cyanide the cyanogen ion is so extremely powerful that the effects of the potassium ion are entirely masked and the action of the compound is indistinguishable from that of other salts of hydrocyanic acid.

The effect of salt action as mentioned above, is due largely to a disturbance of the osmotic balance between the blood and the other tissues of the body. One of the results of this change is an increase in the flow of urine. This occurs because of the greater volume of the blood; for, if a concentrated solution of the salt is introduced into the blood stream, there is a passage of the water from the tissues of the body into the blood in order to reduce the solution of the salt to a concentration isotonic with the normal bodily fluids. If, on the other hand, a dilute solution of the salt is introduced into the circulation, a sufficient amount of water will be retained in the blood to maintain the isotonicity. It follows therefore that saline substances introduced into the circulation whether in concentrated or dilute solutions, tend to increase the volume of the blood and therefore to provoke diuresis. Theoretically, only the water and the foreign salt should be carried off in this diuresis, but, as a matter of fact, it has been observed that the kidney is apparently unable to separate completely the constituents which go to make up the urine and we find that the other solid matters are also increased; therefore, any crystallizable substance—such as sodium chloride, potassium acetate, sugar or urea—which is not too highly toxic to be introduced into the blood in sufficiently large quantities, will tend to provoke diuresis. But it is evident that, if equimolecular weights of two salts are introduced into the blood stream, the osmotic equilibrium will be most disturbed by the one which exists in the blood in smaller proportion, or is entirely foreign to it. Therefore the salts of potassium are more actively diuretic than the salts of sodium because there is a much larger quantity of sodium salts in the blood than of the potassium salts.

### POTASSIUM.

As most of the mineral acid ions (except the chloride) are physiologically active, when the pure potassic effect is desired, the vegetable salts should always be given the preference.

*Potassium carbonate*, the potash of commerce, is obtained from wood ashes and other sources. The crude carbonate occurs in the form of huge stony masses but when purified so as to conform to the U. S. Pharmacopœia it is a white granular powder, very deliquescent, without odor and with a simply alkaline taste. It is soluble in less than its own weight of water but insoluble in alcohol. It is too irritant for general use as an internal remedy.

*Potassium bicarbonate*, which because less irritant is much to be preferred therapeutically to the carbonate, is in the form of transparent colorless crystals, not deliquescent, slightly alkaline in reaction, soluble in about 3 parts of water, almost insoluble in alcohol.

*Potassium hydroxide* is usually found in the form of white or nearly white semi-translucent pencils, very freely soluble in water and in alcohol. It is a very active caustic. It is rarely used internally and then only in the form of the solution.

*Potassium citrate* is found either in crystalline form, or as a white granular powder. It is deliquescent in air, freely soluble in water, sparingly so in alcohol. Its aqueous solution reddens litmus paper, but does not affect phenolphthalein. It is the least offensive to the palate of all the potassium salts except the tartrates.

*Potassium acetate*, which occurs either in crystalline masses or as a white powder, is extremely deliquescent and soluble in less than half its weight of water, also freely soluble in alcohol. Its solution reacts alkaline to litmus, but does not affect phenolphthalein.

*Potassium bitartrate*, or cream of tartar, differs from the other official salts of potassium in that it is practically insoluble in water, requiring 200 times its weight of water (77° F.) to dissolve it. It is acid in reaction, and has a pleasant acidulous taste. On account of the relatively large proportion of tartaric acid present it is an active hydragogue cathartic. (See p. 512.)

#### Official Preparations:

The following are the official preparations whose activity depends chiefly on the potassium ion.

Potassii Acetas.....	15 to 30 grains (1-2 Gm.).
Potassii Bicarbonas.....	15 to 30 grains (1-2 Gm.).
Potassii Bitartras [Cream of Tartar].....	15 to 45 grains (1-3 Gm.).
Potassii Carbonas.....	5 to 10 grains (0.3-0.6 Gm.).
Potassii Citras.....	15 to 30 grains (1-2 Gm.).
Potassii Citras Effervescens (20 per cent.)....	1 to 2 drachms (4-8 Gm.).
Liquor Potassii Citratis (8 per cent.).....	$\frac{1}{2}$ to 1 fluidounce (15-30 C.c.).
Potassii Hydroxidum [Caustic Potash].....	Not used internally.
Liquor Potassii Hydroxidi (5 per cent.).....	
[Liquor Potassæ].....	10 to 20 minims (0.6-1.2 C.c.)

**Physiological Action.**—*Local Action.*—Potassium hydroxide, like other hydroxides, is a powerful escharotic, but many of its vegetable salts are more or less irritant. These salts are also powerful depressants probably of all of the higher tissues.

The mineral salts of potassium appear to be excreted unchanged, whereas the salts formed with vegetable acids, as the acetate, or citrate



(except the bitartrate), are apparently oxidized in the body, being eliminated as carbonates. The great mass of the salt escapes through the kidneys but the studies of Kramer suggest that a small proportion is eliminated by the intestinal glands.

Alfred S. Taylor, obtained from the urine of a patient who was taking two hundred and seventy grains of potassium nitrate daily, 158.7 grains per diem. Rebuteau found that potassium chloride had no effect upon the acidity of urine, but that if the carbonate, acetate or citrate was taken the urine became alkaline. As the last two of these are neutral salts, it is evident that they are converted in the system into an alkaline salt, in all probability into a carbonate.

*Neuro-muscular System.*—Podocaepow believed that the action of salts of potassium in the frog is chiefly upon the muscles, but the experiments of Guttman, of Ringer and Morshead, and of Ringer and Murrell, have definitely proven that the brain, the spinal cord, the motor and sensory nerves, and the muscles are all attacked by potassium. According to Ringer and Murrell, the spinal cord and, next to it, the brain are the most sensitive to the action of the drug.

Astalfoni found that when locally applied to the brain cortex, to the spinal cord, to the peripheral nerves, or to the muscles, the salts of potassium produce a very pronounced lessening of irritability. When very weak solutions were employed this condition of depression was often preceded by one of excessive irritability, but when solutions of five per cent. were used, no such stage was observable.

*Circulation.*—Although there is some evidence that in very small doses the potassium ion has a slight stimulant influence upon the heart, it is not yet proven. On the other hand, it is quite certain that, in full dose, potassium markedly lowers the arterial pressure, and in human medicine this is the only influence of the base upon the circulation which is clinically demonstrable. The fall of pressure is very largely due to the direct action of poison upon the heart, but there can be no doubt that the muscle-fibres of the blood-vessels are also depressed, so that the blood-pressure is reduced by the conjoint depression of the muscle-fibres of the heart and blood-vessels. This action is shown by Dogiel to be a portion of the wide-spread general muscular influence of the poison, the heart muscle and the arterial muscle-fibres being simply more sensitive to the influence of potassium than are the skeletal and intestinal muscles. The heart is usually arrested in diastole (Podocaepow and Guttman), and as pointed out by Traube, its muscle may be unable to respond to electrical stimulation.\*

Traube asserts as the result of his experiments that, injected into the blood in doses of two or three grains, potassium nitrate produces a fall in the pulse-rate and a rise in the arterial pressure. Aubert and Dehn have experimented with a number of the salts of potassium, and found that, with the exception of the permanganate, they all act upon the circulation in the manner just described. It remains at present writing, however, doubtful whether the rise of pressure just spoken of is a direct

\* The poisonous influence of potassium upon the heart was, we believe, first discovered by Black (*C. R. S. B.*, 1839), and has been abundantly confirmed.

phenomenon caused by potassium. No dose of a potassium salt ever calls forth symptoms of circulatory stimulation from the human body. Further, Podocae-pow and also Aubert and Dehn affirm that the rise following the potassium injection in the animal usually lasts only three minutes, and that in no case is the maximum effect perceptible for more than ten minutes. Aubert and Dehn further assert that there is no cumulative action, the repetition of small doses of the drug at brief intervals leaving no residual effect, the pressure returning to the normal after each injection, just as though no previous injection had been given. The correctness of this statement remains doubtful, since Guttmann asserts that there is a gradual rise of pressure.

If there be a rise of pressure produced by the minute doses of potassium it would seem probable that it is due to an action upon the blood-vessel walls, since Boltazi found it impossible by any dose to increase the work done by the frog's heart; and in the experiments of Astalfoni, perfusion of minute doses of potassium through the blood-vessels of the kidney or of one exsected leg caused contraction of the arterioles.

The method by which the changes in the pulse are produced by the small dose of potassium also remains uncertain. Traube affirms that if the vagi be cut after exhibition of potassium, the lessened pulse-rate instantly becomes rapid, and the already increased arterial pressure rises still further. The same observer also found that after section of the pneumogastrics small doses of the nitrate produced a fall in the pulse, with increased arterial pressure; but on a repetition of the dose in the same animal no lessening of the pulse-frequency was perceptible, while each time the pressure rose. This seems to indicate that the cardiac action of the drug is independent of the inhibitory apparatus, which is confirmed by the experiments of Aubert and Dehn upon atropinized dogs, and the work of Guttmann, who found that vagal section had no influence on the course of the poisoning.

According to Aubert and Dehn, for a few seconds before complete suspension of cardiac movements there are irregular, "stormy" convulsions, which run through the heart in a sort of peristaltic manner with great rapidity, but have no effect in expelling the blood.

The observations of Aubert and Dehn, that the effect of potash is not permanent unless it is continued a certain length of time, is in accord with that of Astalfoni, who found in using it locally that functional irritability could be restored by washing out the part with a weak solution of sodium phosphate. Podocae-pow and Guttmann have found that in fatal poisoning the contractility of the cardiac muscle may be in a measure preserved if the potassium had been very slowly introduced into the circulation.

*Nutrition.*—It seems to be clearly demonstrated that potassium increases the elimination of nitrogenous matter with the urine in both health and disease. It is well known that potassium increases oxidation outside of the body and its effect in hastening the katabolic changes appears to be dependent upon its oxidizing power.

In an elaborate series of experiments upon himself, E. A. Parkes found that liquor potassæ (two fluidrachms) when taken fasting, produced in from thirty to ninety minutes an increased flow of slightly acid urine containing the whole of the alkali and organic matter which differed in quality from that ordinarily found in urine, and was also larger in amount than normal. Golding Bird found in a dog, that three drachms of potassium acetate increased the uric acid about thirty-two per cent.; the urea, about sixty per cent.; extractives, including kreatine, kreatinine, etc., about twenty per cent. Rabuteau found that the daily ingestion of seventy-five grains of potassium chloride caused an increase of twenty per cent. in the amount of urea discharged. Aug. Dehn has also experimentally found that the potassium salts greatly increase the elimination of urea.

The conclusion reached by experimental research made upon healthy men and animals—namely, increased tissue-change as the result of potassium ingestion—have been found to apply in disease.

In six observations upon subjects affected with what may be termed indifferent diseases, such as lead palsy, Parkes found that the urea was increased, and also the sulphuric acid, by the use of drachm doses of liquor potassæ. Austin Flint has studied the effect of potassium nitrate upon a number of persons suffering from various diseases, and found that it very greatly increases the amount of solids in the urine. In rheumatism Parkes found that liquor potassæ increased the elimination of sulphuric acid, but had no decided influence on the uric acid. He, however, used such small doses of the drug as not to get the effect obtained in the alkaline treatment of the disease, since he expressly states that the urine remained acid.

Basham affirms, however, that as the result of a series of analyses he has found that in uric acid diathesis not only is there a great increase of the urea during the use of potassium, but also that the uric acid, either free or combined, in the urine is greatly diminished. Basham, remembering that Schunck had proved that, under the oxidizing power of potassium, uric acid outside of the body is converted into oxaluric acid, which in its turn is readily metamorphosed into oxalic acid and urea, carefully examined the urine of gouty patients taking the alkali, and found that not only was the urea increased, but that oxalic acid also appeared as the uric acid decreased, and that the urine, on standing, deposited crystals of calcium oxalate, although none of these could be found in it when first voided. This research of Basham certainly seems to demonstrate that in uric acid diathesis the potassium salt increases the oxidation and the ultimate metamorphosis of tissue.

**Therapeutics.**—An important use of the vegetable salts of potassium is in *acute inflammatory rheumatism*. Before the introduction of the salicylates the alkaline treatment was the best that was known for cases of thoroughly acute *rheumatism*. This consists in the use of either the acetate or citrate of potassium with or without sodium or potassium bicarbonate. The medicine must be given freely, an ounce to an ounce and a half in the day, in sufficient dose to render and keep the urine alkaline. Opium may be at the same time employed in as large doses as are required to relieve the pain. After a few days, when the violence of the symptoms has abated and decided anemia appears, the exhibition of the drug should be discontinued and potassium iodide, with tonics, be substituted. In cases subacute from the beginning a combination of the potassium iodide and acetate is sometimes very efficient, ten grains of the former and thirty of the latter being administered three or four times a day. The potassium probably does good in rheumatism by lowering arterial action, by favoring oxidation and elimination of partially effete materials, and by neutralizing excessive acidity.

As depurants, the salts of potassium are very useful in various diseases. Attention has been especially called by Golding Bird to their value in that class of cases spoken of as *chronic biliousness*. In *chronic malarial poisoning*, in *catarrhal jaundice*, and in the *jaundice* of simple *hepatic torpor* they are often of use. In *uric acid gravel* and *uric acid calculus* the vegetable salts are useful in checking the deposition of the uric acid, but have no influence upon calculi already formed.



The bitartrate appears to differ from the others vegetable salts in being eliminated unchanged. An ounce (30 Gm.) of it in a pint of infusion of juniper-berries, taken, in divided doses, during the twenty-four hours, will very often act most happily in *dropsy*. In acute *desquamative nephritis*, potassium bitartrate is often very serviceable; as, however, the avoidance of irritation of the kidneys is imperative in this disease, the infusion of juniper should not be used.

**Administration.**—As usually exhibited, the salts of potassium are exceedingly distasteful. There is no need of this whatever. The citrate dissolved in lemon-juice is entirely palatable. Still more pleasant is the effervescent potassium citrate of the U. S. Pharmacopœia; this is, however, more distinctly laxative in its action on account of the sodium tartrate resulting from the reaction which causes the effervescence.

POTASSIUM NITRATE (*Potassii Nitrās*), or *Nitre*, is ordinary salt-petre. It occurs in more or less perfect, long, striated, semi-transparent, six-sided prisms, with dihedral summits, or a white crystalline powder; of a sharp, saline, somewhat cooling taste; containing no water of crystallization, but decrepitating when thrown on the fire, from the evaporation of water mechanically retained in the cervices of the crystals; soluble in 3.6 times its weight of water, insoluble in absolute alcohol.

**Physiological Action.**—Potassium nitrate is so violently irritant that the general effects of the potash in it upon the system are lost in the local symptoms caused by its overdose. It probably exercises a direct irritant action on the kidney as well as a salt action. On account of these properties it is vastly inferior to the vegetable salts of potassium, as a depurant, but is still occasionally used as a diuretic in cardiac *dropsy*.

**Toxicology.**—The symptoms of poisoning by potassium nitrate are an intense burning pain in the stomach, coming on in a few minutes after the ingestion of the poison, and soon followed by violent vomiting, and, it may be, free purging, with, after some hours, collapse, great muscular weakness, and not rarely local convulsive tremblings. The matters vomited, and even the stools, may be bloody (Husemann). Sometimes the nervous symptoms predominate, and the purging may be absent: collapse, with slight vomiting and with or without paralysis of the lower limbs, may alone exist. Suppression of urine has been noted in some cases.\* After death, very grave lesions are found in the stomach and the intestines, such as intense redness and congestion, and effusion of blood into the sub-mucous coat, and sometimes into the stomach itself. Even ulceration and corrosion of the mucous membrane have been observed. How far potassium nitrate acts upon the blood is at present uncertain; Mairet and Combemale assert that it alters the red blood-

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\* Case, *Pharmaceut. Journ.*, Feb. 1846, 356.

corpuscles. Sometimes, however, death has occurred, in poisoning by saltpetre, with great suddenness. In the only cases of this character, the record of which we have read, the dose has been very large, and it is possible that the death has been the result of the paralyzing action of the potassium upon the heart.

In the treatment of poisoning by saltpetre, after the stomach and bowels have been emptied, the usual means for the relief of toxic gastro-enteritis should be resorted to.

POTASSIUM CHLORATE (*Potassii Chloras*) occurs in white rhomboidal plates of a pearly lustre or a white granular powder, of an acerb taste, soluble in 16 parts of water, insoluble in alcohol.

#### Official Preparations :

Potassii Chloras. ....	5 grains (0.3 Gm.).
Trochisci Potassii Chloratis .....	each 2½ grains (0.15 Gm.).

**Physiological Action.**—Locally, this salt is irritant and astringent. The physiological action of potassium chlorate is evidently dominated by the acid radical. S. J. Meltzer found that the injection of three to four minims of its five-per-cent. solution produced immediate violent convulsive disturbances, with coma, and that similar symptoms were caused by the sodium chlorate, and it is evident that both salts act directly upon the nerve-cells.

The theory that potassium chlorate yields its oxygen in the system is absurdly untrue.\* The potassium chlorate escapes unchanged chiefly with the urine, but also in the saliva, and probably all the secretions of the body.

Isambert found it in the tears, the bile, the nasal mucus, and even in the milk of nursing women. Rabuteau, Isambert and J. von Mering have each recovered from ninety to ninety-nine per cent. of the ingested salt from the urine. Indeed, Marchand, in experiments upon the lower animals, asserts that he has recovered all of the ingested chlorate from the secretions, and we must conclude that it practically all escapes from the body unchanged.

Von Mering in one or two instances in the dog found a slight increase in the chlorides of the urine during the administration of the chlorate, and it is possible that a minute quantity of the chlorate does undergo deoxidation; but it must be considered established that any such change, if it occurs at all, affects so small a portion of the drug as not to be worthy of consideration.

The therapeutic dose of potassium chlorate produces no sensible effects in the system. Isambert found that, when taken by himself in doses of from two to five drachms, it caused salivation, free diuresis, increase of the appetite, and, when not well diluted, gastric irritation; the urine continued strongly acid, and contained an excess of rosacic acid, uric acid, and the urates.

**Therapeutics.**—There is no systemic effect of potassium chlorate which justifies its use as an internal remedy. On account of its strongly irritant effects on the kidneys it should never be used

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\* For detailed discussion, see tenth edition.

for its salt action as a diuretic. The only use for which it is suitable is as a local stimulant in inflammations of mucous membranes, especially of the mouth. In the *follicular* or *aphthous stomatitis* of children \* it is almost a specific. In ordinary *sore throat* or *angina* a solution containing three to four per cent. of potassium chlorate with fifteen to twenty-five per cent. of the fluidextract of *rhys glabra* is, as a gargle, most effective.

In chronic *dysentery* and other diseases of the colon it may be applied by means of the large enemata. In *hemorrhoids* the injection, when the patient goes to bed, of half to one ounce of its saturated solution, combined with a few drops of laudanum to secure retention, is often of the utmost service. In *stomatitis* it is best employed in the form of the troche.

**Toxicology.**—As a poison it has frequently caused death.† The smallest fatal dose is not known, but half an ounce has killed. A drachm taken during a night has killed an infant a year old, and three drachms a child three to four years old. The symptoms may be acute or subacute. In the rapid cases there have been violent vomiting, profuse diarrhœa, excessive dyspnœa, great failure of the heart's action, and marked cyanosis. In the subacute cases the gastro-intestinal symptoms have been severe, with generally vomiting of blackish-green matters and distinct swelling of the liver and the spleen. The urine is markedly lessened in quantity, albuminous, often of an opaque reddish-brown or blackish color, and showing under the microscope brownish or yellowish-brown tube-casts, frequently containing the detritus of blood-corpuscles. Hemoglobinuria has been noticed,‡ and methemoglobin is a common symptom. The nervous symptoms have been severe delirium, coma, tonic and clonic cramps, and a peculiar stiffness of the extremities.

Headache, loss of appetite, violent pains in the abdomen and other portions of the body, and marked abdominal tenderness have usually preceded the loss of consciousness. Not rarely there are minute ecchymoses upon the surface of the body, and even more frequently there is a general jaundice. In some cases the patient has rallied and seemed to be on the road to recovery when the fatal relapse has occurred.

After death the blood is usually chocolate-colored, the gastro-intestinal tract is inflamed, the liver and spleen are enlarged and filled with the brownish débris of red blood-corpuscles, the bone-marrow and the brain are often similarly colored, while the mucous membranes are usually swollen and ecchymosed. The kidneys are profoundly affected, their tubules full of brownish casts and their epithelial structure evincing a nephritis. The most characteristic

\* Laborde (*Bull. Thérap.*, 1874, lxxxvii.) and Tacke (*Inaug. Diss.*, Bonn, 1878) have shown that sodium chlorate acts physiologically like the potassium salt; and S. Ringer and H. Sainsbury (*London Lancet*, 1882, ii. 736) have found it equally efficient in *stomatitis*.

† For collection of cases, see *Chlorsäure Kali*, J. von Mering, Berlin, 1885. To Jacobi, of New York, belongs the credit of having first called attention to the dangerous action of this much-abused remedy (*Amer. Med. Times*, April, 1861, 245).

‡ *Trans. Internat. Congress*, 1881, i. 463.



and probably the most important of the lesions is the change in the blood, which was first noticed after death by F. Marchand. L. Riess noted in a case during life that many of the red blood-corpuscles were decolorized, and others contained little granules of an elliptic shape. The changes in the blood are the result of the formation of a substance apparently identical with the methemoglobin of Hoppe-Seyler and characterized by the appearance in its spectrum of a dark line in the red. Methemoglobin is readily produced by mixing either sodium chlorate or potassium chlorate with blood: that it is produced in the body during life has been experimentally proved in cats, dogs, and rabbits by A. Falck, by H. Lenhartz, and by Cahn, and is also shown in man by the wide-spread staining not only of the interior of the blood-vessels, but also of the walls of the whole lymphatic system, found after death from the chlorate. (Case, N. Hammer.)

### LITHIUM.

Lithium is used as a base for the carrying of a number of active acids, as benzoic, salicylic or hydrobromic, but the pharmacopœia recognizes two salts, the carbonate and the citrate, whose usefulness depends upon the lithium ion.

*Lithium carbonate* is a white odorless powder with a somewhat alkaline taste and only sparingly soluble in water.

*Lithium citrate* occurs as a deliquescent white powder, or in colorless crystals. It is soluble in twice its weight of water.

#### Official Preparations:

Lithii Carbonas.....	10 to 30 grains (0.6-1 Gm.).
Lithii Citras.....	10 to 30 grains (0.6-1 Gm.).
Lithii Citras Effervescens (5 per cent.).....	2 to 4 drachms (8-15 Gm.).

When one of the official salts of lithium is ingested absorption begins almost immediately. The lithium has been detected in the urine by Clarence Good ten minutes after the hypodermic injection. Excretion goes on, however, slowly, since the same chemist has found lithium in the urine twenty-three days after the injections had been stopped. The chief channel of escape is through the urine, but excretion occurs also from the salivary and gastro-intestinal glands. No cases of serious poisoning by a lithium salt have been recorded, but we have seen large, repeated doses produce pronounced malaise, with muscular weakness and some disorder of the digestion. According to P. Pergami the exhibition of lithium carbonate distinctly increases the alkalinity of the blood.

According to the studies of Binet, the lithium salts produce in mammals pronounced feebleness, with nausea, diarrhœa, and other digestive disturbance, increasing dyspnœa, fall of temperature, and death, usually preceded by convulsions. Death is said to be due to a direct centric arrest of respiration, although a markedly depressing influence is exerted upon the heart, which is finally arrested in diastole.

When life is maintained by artificial respiration the peripheral nerves become entirely paralyzed and the muscles affected, as is shown by peculiar fibrillary contractions. In poisoned frogs, also, the excitability of the muscles is somewhat diminished.

Lithium salts were originally recommended by Ure and Garrod in the treatment of uric acid *diathesis* and of *chronic gout*; theoretically because it was believed they had the power of dissolving uric acid and the urates. As the dissolving action is, however, only manifest in quantities too great for therapeutic administration and as uric acid, according to modern pathological ideas, plays only a very secondary rôle in *gout* or *rheumatism* it is evident that the value of lithium is slight. It probably exercises some depurant effect similar, but greatly inferior, to potassium. E. Duché affirms that their prolonged local application is very useful in relieving *gouty joints*, and that in *gouty conjunctivitis* frequent washing of the eye with a solution of lithium carbonate, 1 to 500, is effective.\*

**PIPERAZIN.**—*Piperazidine*, or *Diethylendiamine*, occurs in small, glassy, lustrous tables, or, in the form of the *hydrochlorate*, in silky, lustrous, lanceolate crystals.

Because of the fact that uric acid is soluble in solutions of piperazin, while the theory that uric acid as the causative factor in removing conditions was still prevalent it was a remedy which enjoyed a considerable popularity in the treatment of various gouty and rheumatic diseases. It has not, however, proven itself a remedy of great practical value. It may, perhaps, be of some service in cases of uric acid gravel.

Piperazine is rapidly absorbed and eliminated through the kidneys, producing a reddish-brown urine. Concerning its general physiological action there is very little knowledge. The therapeutic dose produces in man ordinarily no symptoms, but we have seen muscular weakness and general depression follow the continuous exhibition of large doses. Whether it does or does not affect the general nutrition is unknown. Vogt asserts that it checks uric acid elimination. Ebstein and Sprague have found that it has no effect either upon the excretion of urea or of uric acid. It has been very largely used in *gout*, but has failed to sustain its first reputation, although in occasional cases it apparently exerts a markedly beneficial influence for a time. It causes too much pain to be used hypodermically; fifteen to twenty grains (1–1.3 Gm.) of it may be administered by the mouth, during the day, in a quart of plain or carbonated water. It is too hygroscopic and too easily decomposed to be given in powder or in watery solution, but the solution of one part in twenty of alcohol and eighty of water is said to be fairly permanent. Van der Klip

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\* *Martineau's Solution.*—Martineau affirms that he has obtained very remarkable results in the treatment of *diabetes mellitus* by the use of a solution of lithium carbonate and sodium arsenate. In *gouty diabetes* this *arsenical solution of lithium* may prove of service: from five to ten grains of lithium carbonate and one-thirtieth of a grain of sodium arsenate may be given three times a day.

has found that in the lower animals, in sufficient dose, it produces vomiting, irregular breathing, general muscular weakness, and relaxation; that it decreases the oxidizing power of oxyhemoglobin and the coagulability of the blood; and that it checks the action of peptonizing ferments.\*

**SUGAR.**—Various sugars, when taken in sufficient quantity to exercise a "salt action," are capable of provoking diuresis. Although not frequently used for this purpose it has been affirmed by S. Meslach, Zavadsky, Germain-Sée, and other clinicians that both glucose and the sugar of milk may often advantageously be used in the treatment of *cardiac dropsy*, *pleuritic effusions*, etc., but are of little value when there is renal disease. The general testimony seems to be that the sugar of milk is the more active of the two. These sugars may be given in doses of from one to six ounces (30–180 Gm.) a day, administered in concentrated syrup or in milk. According to the experiments of Albertoni, all sugars injected into the veins cause a rise of the arterial pressure by a direct stimulation of the heart. He also found that the kidneys, as tested by Roy's oncometer, become congested or swollen.

#### Official Preparations :

Saccharum—Cane Sugar.

Saccharum Lactis—Milk Sugar.

Syrupus (85 per cent.)

### STRONTIUM.

The only official salts of strontium are the bromide, iodide and salicylate which are described under the head of their respective acids. The effects of the strontium ion are here considered.

*Absorption and Elimination.*—Our present knowledge indicates that the soluble salts of strontium are precipitated by the alkalis and phosphates of the intestines, so that they are only partially absorbed; and that elimination is even more slow than absorption; so that strontium has a tendency to accumulate in the liver, in the muscles, and especially in the bones.

Horatio C. Wood, Jr., (confirmed by H. C. Wood and John P. Arnold) determined that when an official salt is administered by the mouth only a minute proportion of it can be obtained from the urine, while a great amount is readily obtainable from the feces. It was further found that when it has been given hypodermically only a minute proportion of strontium escapes with the urine. The research of L. R. Mendel and H. C. Thacher indicates, however, that more of the strontium is absorbed than would seem to be indicated by the results of the earlier investigators. These researches confirmed the results previously obtained, but showed further that when strontium is subcutaneously or intravenously given, a large portion of it can be obtained from the feces, so that elimination must take place in the alimentary canal. It is, however, probable that the strontium found in the feces

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\* H. Hildebrandt (*Berlin, Klin. Wochen.*, 1894) having found that piperazine, even in small quantities, checks the saccharifying influence of hemic and other hydrolytic ferments, although it has no destroying influence, tried the drug in diabetes produced in dogs by phloridzin with pronounced success; so that the remedy is certainly worthy of trial in *diabetes mellitus*.



after the administration of the drug by the mouth represents not only, as believed by Mendel and Thacher, strontium which has been absorbed, but also even more largely strontium which has failed of absorption.\*

**Physiological Action.**—Binet affirms that the continuous use in the lower animals of excessive doses of strontium produces general feebleness with increasing dyspnoea, cyanosis, clonic convulsions, and death from asphyxia. When recovery occurs the motor power gradually returns, with stiffness, ataxic movements, and not rarely with the assumption of bizarre positions.

As was shown by Wood and Arnold, when injected into the bloodstream, the salts of strontium produce a marked slowing of the pulse-rate with a notable increase in the arterial pressure. If the dose is sufficiently large the pulse later becomes rapid and the arterial pressure falls somewhat, although it may not reach the normal. After toxic doses, however, both the pulse-rate and the pressure at last gradually fall to zero. The rise in pressure is due to the conjoined stimulation of the cardiac muscle and also a direct stimulation of the arterial walls. These authors confirm the conclusions of Lauder Brunton, that strontium affects directly the voluntary muscles producing a primary increase of muscular power with a final paralysis. Evidently strontium is a muscle-poison which first stimulates and afterwards paralyzes the muscle-fibres, acting both upon the muscles of the skeleton and upon those connected with circulation; its stimulating effect upon the circulation being, therefore, the result of a wide-spread general influence of the drug upon the muscle-fibres both of voluntary and involuntary life. It is probable, though not proved, that the muscle-fibres in the intestines are also affected by the strontium salt.

According to Binet, in poisoning by strontium, the nerve-centres are more powerfully affected by the drug than are the muscle-fibres themselves, death occurring in the frog from centric respiratory paralysis; the peripheral nerves and the muscles, although depressed, still retaining after death some functional power.

**STRONTIUM LACTAS.**—*Strontium Lactate* occurs as a white granular powder, or in crystalline nodules. It is odorless, of a slightly bitter saline taste, permanent in the air, and soluble in about four parts of water; also soluble in alcohol. According to Germain-Sée, Paul, Dujardin-Beaumetz, and other French clinicians, it is a valuable remedy in the treatment of chronic *Bright's disease*, increasing the amount of urine, diminishing or arresting the excretion of albumin, and improving the general nutrition. In albuminuria due to pulmonary congestion the drug is said to be of service, and it is further affirmed that its influence for good is especially marked in *desquamative nephritis* and much less pronounced in *interstitial nephritis*. In many cases there is no increase in the flow of urine, and the good achieved seems to be due to an alterative influence upon the secreting structure of the kidney. In our own experience the strontium lactate has not yielded results such as are ascribed

\* The presence of strontium phosphate in bone-ash is affirmed by some and denied by other chemists. According to the experiments of Max Cremer, the feeding of strontium phosphate to young hounds has no influence in preventing the development of rickets (*München. Med. Wochen.*, 1892).

to it by the French observers. It is, however, a harmless remedy, whose use should not prevent the administration of other appropriate drugs. The usual dose is from twenty to thirty grains (1.3–2 Gm.), given three times a day in solution; but much larger amounts have been exhibited without producing apparent symptoms.

### ALTERATIVE DIURETICS.

Under the term of alterative diuretics are included a number of drugs which are used chiefly for their effect upon the mucous membranes of the urinary tract. Most of these substances contain principles which are more or less antiseptic in their action. Many of them, however, unite to this antiseptic action, a local stimulant effect, which makes them useful especially in chronic inflammations. Those of the alterative diuretics such as turpentine and juniper, which contain irritant principles, will in a healthy kidney increase the secretory activity, but their use for this purpose is comparatively infrequent.

### BUCHU.

The leaves of *Barosma betulina*, a native of Southern Africa. These leaves are an inch or less in length, from three to five lines broad, of various forms, but always notched on the edges, and having a strong, rather rank, yet somewhat aromatic odor, and a warm, bitterish taste. They owe their virtues, which they yield to water and to alcohol, to a volatile oil and a bitter extractive.

Fluidextractum Buchu.....1 fluidrachm (4 C.c.).

**Therapeutics.**—Buchu is a mild stimulant and alterative to the mucous membrane of the genito-urinary organs, useful in *sub-acute* and *chronic cystitis*, *chronic pyelitis*, and *irritation of the bladder*. Its oil is undoubtedly absorbed, and is eliminated by the kidneys, to whose secretion it imparts its odor. In *irritated bladder*, when the urine is highly acid, and when there is a constant desire to urinate, with but little relief from micturition, buchu, in combination with a vegetable salt of potassium and the sweet spirit of nitre, often gives great relief.

### UVA URSI.

*Bearberry* is the leaves of *Arctostaphylos Uva-ursi*, a low evergreen shrub, indigenous to northern maritime Europe, and also to our northern coasts as far south as New Jersey. They are from half an inch to an inch in length, wedge-shaped, thick, coriaceous, with a smooth, rounded margin. The odor is hay-like, the taste bitterish. astringent, and somewhat sweetish. The most important constituent of uva ursi is the glucoside *arbutin*, which occurs in long acicular colorless crystals, freely soluble in water, less so in alcohol and in ether, and is resolved by the action of sulphuric acid into glucose and *hydrochinone*.

Fluidextractum Uvæ Ursi.....2 to 4 fluidrachms (8–15 C.c.).

**Therapeutics.**—*Uva ursi* has been long used in medicine for its influence upon the genito-urinary mucous membrane, and at present is employed only in chronic *pyelitis*, *cystitis*, and other affections of the genito-urinary mucous membrane, when a slightly stimulant and an astringent action is desired. Hughes found that in doses of one grain *arbutin* is a powerful diuretic. It seems to be free from poisonous properties, as Jablonowski took in forty-eight hours eighteen grammes of it without discomfort. It produces a discoloration of the urine varying from pale greenish to dark greenish brown, the color deepening upon standing due, as has been shown by Von Mering, by L. Lewin, and by Steffen to the formation of hydrochinone. The change probably occurs in the kidneys, as *arbutin* is free from toxic properties, while Brieger has shown that hydrochinone is poisonous. The experiments of Forster show that hydrochinone \* is a powerful disinfectant and antiferment. It is stated that a one-per-cent. solution will arrest putrefaction and alcoholic fermentation, while one-half per cent. is sufficient to check butyric fermentation. Concerning the therapeutic value of *arbutin* there has been much discussion, but the fact that it has failed to come into general use indicates that it has little practical effect, and that H. Laurentz was right in asserting that *uva ursi* is of value in genito-urinary diseases chiefly on account of its tannic acid and of the volatile oil which it contains.

**PAREIRA.**—*Pareira Brava* is the root of *Chondrodendron tomentosum*, a climbing plant of South America. There appear to be in the root one or more alkaloids.† *Pareira Brava* has been used with asserted advantage in *cystitis*, in *irritable bladder*, and in *chronic gonorrhœa*, and appears to exert a stimulant action upon the mucous membrane of the whole genito-urinary apparatus.

Fluidextractum Pareiræ . . . . . 1 fluidrachm (4 C.c.).

**CHIMAPHILA.**—*Pipsissewa* is the dried leaves of *Chimaphila umbellata*, a little indigenous perennial, distinguished from its inert congener *C. maculata* by the uniform glossy green of its leaves. It contains tannic acid, bitter extractive, and, according to Samuel Fairbank, a crystalline principle, *chimaphilin*. *Pipsissewa* is nearly equivalent to *uva ursi* in its therapeutic value, though not so effective.

\* According to the experiments of Brieger, *hydrochinone* produces in man giddiness, ringing in the ears, and lessening in the force and frequency of the pulse. In the experiments of P. J. Martin (*Therap. Gaz.*, 1887, 289), it caused in the frog violent convulsions, followed by paralysis and death through failure of the respiration, both convulsions and paralysis being the result of a direct influence upon the spinal cord. Small doses in the mammal produced stimulation of the vaso-motor centres, this, if the dose were sufficient, was followed by a depression. The bodily temperature was lowered by large doses from an increase of heat-dissipation, probably the result of a vaso-motor paralysis. H. G. Beyer, after experimenting upon the frog and terrapin (*Amer. Journ. Med. Sci.*, April, 1886), came to the conclusion that hydrochinone affects both the heart and the vessels as a paralyzant, lessening the rate of the heart and the amount of work done, and causing dilatation of the arterioles. Antaeff has found that if two per cent. of hydrochinone be added to fresh urine the latter will remain for many days without undergoing alkaline fermentation, but that if hydrochinone be added to a solution of urea a rapid decomposition of the urea occurs, which Antaeff believes to be the result of a direct chemical action of hydrochinone on urea (*Lancet*, April, 1887).

† See *U. S. Dispensatory*, 19th ed.



Fluidextractum Chimaphilæ.....1 fluidrachm (4 C.c.).

**TRITICUM.**—The rhizome of *Agropyron repens* or couch-grass of Europe and the United States, is believed by many surgeons to have a sedative influence upon the genito-urinary organs, and has been considerably used in *irritable bladder* and *cystitis*.

Fluidextractum Triticæ.....2 fluidrachms (8 C.c.).

### TURPENTINE.

The United States Pharmacopœia recognizes under the title turpentine (*Terebinthina*) the concrete oleoresin obtained by incising *Pinus palustris* and other species of pine; and under the title of CANADA TURPENTINE (*Terebinthina Canadensis*), the liquid oleoresin commonly known as Canada balsam which is the product of *Abies balsamea*, or American Silver Fir, a beautiful evergreen indigenous to the extreme Northern United States and to the British provinces. It is a thick and viscid but clear, yellowish liquid, which by age and exposure becomes converted into a hard, brittle, translucent, resinous mass. Canada Balsam is very rarely, if ever, used in medicine, but resembles turpentine in its action on the system: when fresh it contains about twenty per cent. of the volatile oil, which is its active ingredient.

Turpentine, or, as it is sometimes called, White Turpentine occurs in yellowish opaque brittle masses practically insoluble in water but completely soluble in alcohol. It is rarely, if ever, itself used in medicine, but by distillation is separated into a volatile oil and a resin (*Rosin*), which is official under the name of *Resina*.

The oil of turpentine is a yellowish, highly inflammable oil, of a strong peculiar odor and a hot biting taste, moderately soluble in alcohol, freely so in ether, very slightly so in water. By heating with hydrochloric acid it is converted into a red liquid and a white crystalline substance, which, from its resemblance to camphor, has received the name of *artificial camphor*. Turpentine oil is remarkable for having the property of absorbing oxygen and converting it into ozone.\*

#### Official Preparations:

The official preparations containing the oil of turpentine are:

Oleum Terebinthinæ.....Not used internally.  
Oleum Terebinthinæ Rectificatum.....5 to 15 minims (0.3–1.0 C.c.).  
Emulsum Olei Terebinthinæ (15 per cent.)...1 fluidrachm (4 C.c.).  
Linimentum Terebinthinæ (35 per cent.)....External use only.

The following are the preparations of rosin:

Ceratum Resinæ [Basilicon Ointment].....External use only.  
Ceratum Resinæ Compositum.....External use only.  
Ceratum Cantharidis.....External use only.  
Linimentum Terebinthinæ.....External use only.

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\* For a study of the effect of the ozonizing turpentine oils, see Pallop (*Dorpat Thesis*, 1889).

**Physiological Action.**—Locally, oil of turpentine is a powerful irritant, causing in a very short time inflammation in any tissue with which it comes in contact. It has been asserted that oil of turpentine is a powerful bactericide; but the experiments of Koch and of Christmas-Dirckinck-Holmfeld appear to show that its general antiseptic properties are feeble. It appears, however, to be especially antagonistic to the *Bacillus typhosus*.

When taken by a healthy person, in moderate doses, it produces a sense of warmth in the stomach, soon followed by exhilaration, and, if the amount be sufficient, giddiness and even a species of intoxication. The pulse is increased in force and frequency. The turpentine escapes from the body through the lungs and kidneys, imparting its own odor to the breath and that of violets to the urine.

**Circulation.**—The investigations concerning the systemic effects of oil of turpentine indicate that the European oil differs markedly in its properties from that of the American markets. The turpentine oil of Europe appears to be a stimulant to the medulla, especially the vaso-motor and cardio-inhibitory centres. On the other hand, the American variety has little action on the circulation unless given in very large dose, in which case, it is depressant to the heart.

R. Kobert, using the European turpentine, found that in moderate doses it exerted a powerful stimulating influence upon the inhibitory reflex centre, and also elevated the blood-pressure by stimulating the vaso-motor centres. Very large doses appeared to paralyze both of the centres spoken of, causing decided fall in the arterial pressure. The respiration was first increased in frequency, but later very much diminished. The blood became very dark, and the heart was finally paralyzed. It is said that these results are in accord with those previously published by Azary in the Hungarian language, and Hoppe concludes as the result of his own experiments, presumably made with European oil of turpentine, that the vaso-motor nerves are very early influenced by the drug.

On the other hand, in a series of experiments made in the laboratory of the University of Pennsylvania by H. A. Hare with American oil of turpentine, it was found impossible to produce any marked rise in the arterial pressure. Large doses produced a pronounced fall of arterial pressure, with great cardiac depression, to which, indeed, Hare attributes the fall of the blood-pressure. Doses which had no effect on the blood-pressure increased the frequency of the pulse by an action upon the heart itself. When large doses were administered the pulse became slow,—probably, as Hare believes, as the result of stimulation of the pneumogastric nerves, since section of these nerves was followed by the normal rise in pulse-frequency.

**Nervous System.**—F. Fleischmann found that two drops produced paralysis in the frog,—first of voluntary and afterwards of reflex activity; in the cat and in the rabbit, toxic doses abolished reflex activity, but caused violent lethal convulsions. The preservation of voluntary movement in the frog after the loss of reflex activity, which has been confirmed by Hare, indicates that toxic doses of turpentine paralyze the sensory nervous system, either in the cord or in the peripheral nerves.

**Kidneys.**—The irritant action of turpentine upon the kidneys and genito-urinary tract is very decided. When moderate doses (ten

minims every three hours) of turpentine are taken, there are usually no renal symptoms produced, except a slight increase of the urine. Somewhat larger amounts, when exhibited, are likely to give rise to aching in the loins and to frequent micturition, with perhaps urethral pain accompanying the act. If still larger quantities are ingested, these symptoms are intensified, and at the same time the secretion of urine is diminished. After very large repeated doses of the drug, the aching in the loins is very great, often with spasmodic pain in the ureters; a constant desire to pass water struggles with the inability to micturate, caused by the urethral spasm; the urine is very scanty, albuminous, and even bloody; priapism may be present, and an intolerable irritation may affect all the pelvic organs.

**Therapeutics.**—Externally the oil of turpentine is very much employed as a powerful counter-irritant. It is useful more especially when it is desired to act upon a large extent of surface. When a very intense permanent local impression is required, a blister is to be preferred. Thus, in *pleurisy* a blister may be used, in *bronchitis*, turpentine stupes. In preparing the latter the turpentine should first be warmed by setting the vessel containing it in hot water, then a piece of flannel, just previously saturated with hot water and wrung out as dry as possible, should be dipped in the turpentine and again wrung out. It is then ready for application, and may be left on from fifteen minutes to half an hour, according to the sensitiveness of the skin. For milder effects it may be advantageously applied in the form of the liniment.

Another local use of the oil of turpentine is as an addition to enemata. From a teaspoonful to a tablespoonful of it mixed with double its amount of olive oil renders opening enemata much more active, especially in causing the expulsion of flatus. Turpentine enemata containing much of the oil in a small bulk are also constantly used with good effect in arousing the system from stupor arising from narcotic poison or similar causes.

In *ulceration of the bowels* turpentine taken by the stomach is often very efficient, probably acting locally in the intestine, and in old gastric ulcers good results are sometimes derived from its use. In a single large dose (one-half to one fluidounce, with an equal amount of castor oil) it is an efficient vermifuge. It may also be used as a stimulant in *low fevers*, particularly when the tongue is dry and red.

In *typhoid* or *enteric fever* it without doubt acts as a local stimulant to the ulcerated bowel, besides influencing the general condition of the system. There are two conditions or stages in the diseases named in which it is especially useful,—indeed, is of incalculable service. About the end of the second week the tongue sometimes becomes very dry, red, chapped, perhaps coated in the centre with a brownish fur, and at the same time marked meteorism develops. Ten minims (0.6 C.c.) of turpentine every two hours during the day and every three hours during the night will in the majority of cases remove the bad symptoms noted. That the action of the oil is largely



a local one is shown not only by the arguments of the introducer of the practice, George B. Wood, but also by the value of the same treatment when diarrhœa persists after the acute stage of the fever has passed. When convalescence is protracted, when there is a constant tendency to the recurrence of diarrhœa,—when, in other words, the ulcers of Peyer's patches are slow to heal,—turpentine acts almost as a specific. These clinical results have received scientific confirmation in the work of Theo. Omelchenko, who finds that the bacillus of typhoid fever will not develop in air containing diluted vapor of turpentine, and dies when the atmosphere is saturated with the vapor. Thymol appears to be even more active than is turpentine.

In *typhoid bronchitis* and *pneumonia*, especially as intercurrent in typhus fever and similar diseases, turpentine applied externally and taken internally is often very useful. The same may be said of the low forms of *puerperal fever*. In this disease the abdomen should be kept covered with fomentations of the oil and of warm water alternately, the counter-irritant being used as constantly as a proper regard for the skin of the patient will allow. Internally it should be given in very large doses (ten to fifteen minims (0.6–1.0 C.c.) every two hours).

In *hemorrhages* from the stomach, bowels, or lungs, turpentine has acquired celebrity, but it is hardly so much used as formerly. It is in the ataxic cases that it is useful. We have very rarely employed it. In *purpura hæmorrhagica* turpentine has been highly praised.\*

Oil of turpentine is never employed to increase the flow of urine for the purpose of affecting serous effusions. As a diuretic, it is used solely for its local influence upon the organs. *Excessive diuresis* sometimes is apparently dependent upon a relaxed condition of the kidneys, and under these circumstances oil of turpentine may be of service. *Chronic pyelitis*, *chronic cystitis*, and *gleet* may be benefited by its use.

In giving turpentine in these cases, it should always be borne in mind that, with the exception of cantharides, it is the most actively stimulating of all the diuretics, and must be employed only when such a remedy is called for. In those comparatively rare cases of *urinary incontinence* which are dependent upon debility of the bladder, turpentine is sometimes of great service. When the same symptom is spasmodic, the remedy, of course, is harmful. In absolutely passive *hematuria*, in *impotence*, in certain conditions of *spermatorrhœa*, and in *amenorrhœa*, when great local debility exists, turpentine may be tried with fair hopes of its being useful.

**Toxicology.**—Although several recorded instances prove that turpentine is capable of producing death, cases of serious poisoning by it are rare, and a lethal result is exceedingly so. The symptoms

\* Léon Cruicis has made some experiments which indicate that when turpentine is given in toxic doses to rabbits it increases the coagulability of the blood and gives rise to numerous minute hepatic and pulmonic thrombi.

noted in poisoning by it are most of them constant, but vomiting and purging are present in some cases and not in others. Unconsciousness is generally complete, and occasionally is accompanied by dilated pupils; the urine is very much lessened in quantity, often bloody, not rarely suppressed; the skin is sometimes dry, sometimes moist; the pulse is feeble, rapid, and generally regular.

The lethal dose must be very large, but it is not definitely known, since recovery from four ounces in an infant fourteen months old has been reported. In Maund's case, death was supposed to have been produced in an intemperate woman by six ounces; and Philip Miall has recorded an instance of death caused in an infant fourteen weeks old by turpentine, of which half an ounce was thought to have been taken

### COPAIBA.

This oleoresin obtained from *Copaiba Langsdorffii* and other species of *Copaiba*, large trees growing in Brazil, is a yellowish liquid, of varying viscosity according to age, having a strong, terebinthinate, peculiar odor, and a bitter, burning, disagreeable taste. It mixes uniformly with absolute alcohol and volatile and fatty oils, and is readily dissolved by ether. It contains a volatile oil, a small quantity of soft, viscid resin, about fifty per cent. of a hard, acid resin, and a peculiar crystallizable acid, *copaivic acid*, which, according to Bernatzik, is unimportant, the activity of the drug depending upon the oleoresin.

Oleum Copaibæ..... 8 to 15 minims (0.5-1 C.c.).

**Physiological Action.**—The local action of copaiba is that of an active stimulant or a mild irritant. When taken internally, it yields its active principle to absorption and elimination through the kidneys. The elimination takes place slowly, as Bernatzik found the oil in the urine as much as four days after its ingestion.

Upon the general system copaiba has little influence; eighteen grammes of its volatile oil, taken in three doses during twelve hours, caused only a slight elevation of the pulse-rate and of the temperature, with later vomiting and purging, and still later burning in the urethra and strangury (Bernatzik). In susceptible persons the evidences of the local action of the drug are more marked, it causing decided symptoms of gastro-intestinal irritation, accompanied by marked fever and irritation of the urinary organs, such as strangury, and even almost complete suppression. In Bernatzik's trials fifteen grammes of the resin, taken within five hours, produced violent purging and vomiting, with much abdominal pain.

The discovery in 1841 by G. O. Rey, that the addition of nitric acid to the urine of persons taking copaiba will produce a precipitate resembling that of albumin, has led to much discussion. To obtain this precipitate the copaiba must be freely given. As shown by Bernatzik, the precipitate probably consists of the oxidized oil united

to some urinary principles. The *copaiba-red* of Quinke is a substance found in the urine of persons taking the oil of copaiba; it is an acid, whose salts have the property of reducing the oxide of copper and of polarizing to the left, and may be a source of error in the diagnosis of diabetes. When a pure copaiba resin is used, although the copaiba-red cannot be detected in the urine, the urine still responds to Trommer's test for sugar.

As a stimulant to the genito-urinary mucous membrane, copaiba is distinctly more active than buchu, but less irritating than the oil of turpentine. It may be used in chronic *pyelitis* and *cystitis*, but is chiefly employed in advanced stages of *gonorrhœa*; if administered during the height of the inflammation in these diseases, it is liable to aggravate the symptoms. It is also capable of affecting other mucous membranes than that of the genito-urinary tract, so that it may sometimes be given with advantage in old indolent *ulcers* of the stomach, in *chronic diarrhœa* and *dysentery*, in *advanced bronchitis*, and especially when in *chronic bronchitis* there is very free muco-purulent expectoration. As a local application it is sometimes very advantageous in *chronic chilblains* and other diseases of the skin.

The only preparation of copaiba fitted for internal use is the oil.

### CUBEB.

The unripe, but fully grown fruit of *Piper cubeba*, a climbing plant of Java and other portions of the East Indies. These berries are blackish-veined, about the size of a small pea, and have attached to them a short stalk three or four lines long. Their odor is aromatic and peculiar; their taste warm, camphoraceous, and peculiar. They contain *cubebic acid*, *cubebin*, volatile oil, and resin, and are fully represented by the official oleoresin. Bernatzik has found that cubebin is inert, which is in accord with the statement of Heffter, that cubebin passes through the alimentary canal without absorption, so that it is possible to recover from the feces almost the whole amount ingested.

#### Official Preparations:

Oleum Cubebæ.....	10 to 15 minims (0.6-1 C.c.).
Oleoresina Cubebæ.....	10 to 15 grains (0.6-1 Gm.).
Fluidextractum Cubebæ.....	15 to 30 minims (1-2 C.c.).

Cubeb is a local stimulant which has very little effect upon the general system. In large doses it produces a gastric and genito-urinary irritation proportionate in severity to the amount taken. Like copaiba, it occasionally causes an urticaria, which is probably due to the gastric irritation. It yields to absorption and elimination its active principles, which can be detected in the urine by the addition of nitric acid, when a precipitate resembling that of albumin occurs.

In Bernatzik's experiments ten grammes of magnesium cubebate caused slight acceleration of the pulse and gastric uneasiness, with increased elimination of uric acid. Half an ounce of the oil, taken in thirty-six hours, produced very decided



gastric irritation, with the appearance in the urine of the oxidized oil in the form of a resin, and a very great decrease in the elimination of uric acid. After fifty grammes of the powdered cubeb the gastro-intestinal irritation was most pronounced and the nitric acid precipitate in the urine very abundant.

**Therapeutics.**—Cubeb is used to relieve precisely the same conditions as copaiba. In many cases the best results are to be obtained by the combined employment of the two remedies. It has received much praise as an internal remedy in chronic *hemorrhoids*. It is useful as a local stimulant in the relaxation of the larynx frequently seen in public speakers following slight colds and overuse of the voice, chewing the berries often bringing relief to the throat and tone to the voice. The powdered drug may be used as a snuff in *coryza*. In this disease, as in all others, cubeb should not be employed in the earlier stages before secretion has been established, but later in the affection when the discharge is profuse.

The best preparation for internal use is the oleoresin, which may be given in capsules.

MATICO, the leaves of the *Piper angustifolium* of Peru, contains a volatile oil, resin, and, it is said, a bitter principle, *maticin*. It is a softish mass which is largely employed as a styptic, and probably acts chiefly mechanically, coagulating the blood in its interstices, adhering to the wound, and thus arresting the hemorrhage. It has also been employed in internal *hemorrhages* and in *gonorrhæa*. In these affections it probably acts similarly to oil of turpentine, although much less of a stimulant and much more feeble.

Fluidextractum Matico.....1 fluidrachm (4 C.c.).

JUNIPER is the fruit of the common juniper, *Juniperus communis*, of Europe and this country. These berries are round, bluish bodies, about the size of a large pea, of a sweetish, terebinthinate, aromatic taste. They owe their properties to a volatile oil. They yield to boiling water and to alcohol.

#### Official Preparations:

Oleum Juniperi.....5 to 10 minims (0.3–0.6 C.c.).  
Spiritus Juniperi (5 per cent.)..... $\frac{1}{2}$  to 1 fluidrachm (2–4 C.c.).  
Spiritus Juniperi Compositus (4 per cent.)...2 to 4 fluidrachms (8–15 C.c.).

Juniper is gently stimulant and cordial to the stomach. Upon the kidneys the oil exerts a decided stimulant action, and when freely given is capable of irritating the renal organs above the secreting point, and of producing lessened secretion, strangury, and even suppression of urine. Juniper is largely used as an adjuvant to potassium bitartrate or the alkaline diuretics. On account of its stimulant local influence upon the alimentary canal, it renders the cream of tartar far more acceptable to the stomach, and at the same time aids its diuretic action. Sometimes juniper is employed for its stimulant action on the mucous membrane of the genito-urinary organs in

*chronic pyelitis* and in *chronic catarrh of the bladder*. In the form of the compound spirit or its equivalent, *gin*, juniper is often useful in the subacute *congestion of the kidneys* frequently seen in old persons, and characterized by aching in the loins and lessened urinary secretion without more serious symptoms.

**OIL OF ERIGERON.**—*Erigeron Canadensis*, or *Canada Fleabane*, contains a large proportion of a yellowish volatile oil (*Oleum Erigerontis*) of a rather pleasant odor and taste, which has properties resembling those of turpentine, but much less stimulating. It may be employed in affections of the *genito-urinary organs* and in passive *hemorrhages*. It is especially valuable in *menorrhagia*. According to Starke, it is very efficacious in *gonorrhæa*. The dose is five to twenty minims (0.3–1.2 C.c.) every two or three hours, and is best administered on sugar.

**OIL OF SANTAL** (*Oleum Santali*) is a pale yellowish, strongly aromatic volatile oil, of a pungent, spicy taste, from the distillation of the wood of *Santalum album*. It is insoluble in water, but readily soluble in alcohol. When pure, it is a local irritant and probably capable of affecting the general system, although its physiological action has not been properly investigated. S. Rosenberg has noticed after doses of sixty drops a day irritation of the alimentary canal, burning in the urethra during urination, and an eruption of small red prominences upon the entire surface of the body, involving even the conjunctiva. Oil of sandal-wood is efficient in *chronic bronchitis* and in the advanced stages of *acute bronchitis*, but its most popular use is in *gonorrhæa* after the first period of acute inflammation. From ten to twenty minims (0.6–1.2 C.c.) of it may be given, in capsule or emulsion, three or four times a day.

**KAVA.**—The root of *Piper methysticum* is used in the Sandwich Islands as the basis of an intoxicating liquor known as *kava-kava*, *kava*, or *ava*. It contains a crystalline principle analogous to piperin, which its discoverer, Goble, called *methysticin*, besides an acrid resin, *kavin*, and a volatile oil.

L. Lewin finds that when the kava resin is injected into the frog it produces a very pronounced loss of sensation at the point of injection, due to a paralysis of the peripheral endings of the sensory nerves, and that after the absorption of the remedy there is loss of voluntary motion and reflex activity, which is chiefly of spinal origin. In experiments made upon the warm-blooded animals he obtained similar phenomena,—namely, local anesthesia at the point of injection, followed, after absorption, by general paralysis, due to a direct depression of the motor side of the spinal cord, the motor nerves and the muscles remaining intact. According to Dario Baldi, the active principle of kava produces in the dog a very short period of excitement of the sensory nerves, followed by a complete paralysis, at a time when the whole motor system still responds to stimuli.

In small doses kava is said to act as a stimulant tonic, but when taken in large amounts to produce an intoxication which differs from that caused by alcohol in being silent, drowsy, and without emotional exaltation. The great loss of muscular power which is said to follow kava debauch in those unaccustomed to the use of the drug shows that its influence upon the spinal centres in man is the same as in other mammals. According to Baldi, Randolph, and Lewin, the resin of kava

is a local anesthetic of extraordinary persistency of action, but it appears to be too irritant for practical use. A decoction of the root is used in Oceanica very largely in the treatment of *gonorrhœa*, and its value has been strongly affirmed by Sanné. The dose of the root itself, given in *decoction*, is half a drachm (2 Gm.) three or four times a day: of a *fluidextract*, half a fluidrachm (2 C.c.).

**YOHIMBINE.**—This alkaloid is obtained from the bark of *Corynanthe yohimbi*, a rubiaceous tree, growing in the southern Cameroons district in Africa.

It was originally investigated by Oberwarth and Loewy, who found it was in animals and also in man a very active excitant to the sexual organs and functions. On the other hand, Kravkoff, as the result of experiments upon the lower animals and upon man, concluded that it has no aphrodisiac effect; and frequently produces nausea, salivation, irritability, and other disagreeable results. It has been used, however, by numerous clinicians in neurasthenic *impotence*, with reports which are generally favorable to its influence. (For literature see Merck's Report, 1901, 1902.) It is said to be of no value when impotence depends upon organic nerve trouble, and to be harmful when it is caused by chronic inflammatory disease of the sexual organs or of the prostate gland. Dose, one-twelfth grain (5 Milligm.) of the hydrochlorate, either in tablet or solution, three or four times a day, hypodermically.

### HEXAMETHYLENAMINE.

Hexamethylene-tetramine, is a condensation product of ammonia and formaldehyde. It is largely employed in medicine under various trade names, as urotropin, formin, aminoform, cystogen, etc. It occurs as colorless, odorless crystals, with a bitterish sweet taste, freely soluble in water, moderately soluble in alcohol, and with alkaline reaction. When gently warmed with dilute acid it is decomposed into formaldehyde and ammonia.

**Physiological Action.**—*Local Action.*—*Absorption and Elimination.*—Hexamethylenamine is distinctly irritant. It is absorbed with great rapidity, having been detected in the urine ten minutes after its ingestion, and is eliminated from the kidneys in great part unchanged, although, as first stated by Loebisch, it is to some extent decomposed in the organism with the liberation of formaldehyde.

Casper injected urotropin under the skin of a rabbit and found formaldehyde in the blood, and also was able in some cases to detect formaldehyde in the urine of persons taking urotropin, an observation which has been confirmed by Suter, and by Citron. In a number of cases, however, these chemists failed to detect any formaldehyde in the urine, and P. J. Cammidge could not get it at all; so that it is evident that elimination of formaldehyde after the ingestion of hexamethylenamine is an inconstant phenomenon. It has been suggested that hexamethylenamine is decomposed by the acid juices of the stomach, but Suter found that when he put formaldehyde into the stomach of the rabbit, or took formaldehyde himself in safe dose, it was impossible to detect it in the urine; so that any formaldehyde liberated by the hexamethylenamine in the stomach would in all probability either be distributed in the system or thrown off in some other form than formaldehyde.

It has been shown by Suter that when urotropin is mixed outside of the body with acid urine it undergoes decomposition, although this does not occur when the urine is alkaline. It is therefore probable that that portion of ingested hexamethylenamine which is decomposed suffers change in the kidney and upper urinary passages; a conclusion which is confirmed by an observation of Casper, that when the urine of a person who has taken urotropin is allowed to stand a continuous formation of formaldehyde goes on in it for days.



The bactericidal influence of hexamethylenamine in the urine is not altogether dependent upon its conversion into formaldehyde, since Cammidge has shown that it has itself very marked bactericidal powers.

**General Effects.**—The ordinary therapeutic dose of hexamethylenamine produces no general symptoms, and we know of no cases of poisoning by it. In the dog the daily dose of two hundred and eighty grains is said to cause no other disturbance than renal irritation (Nicolaier). The ingestion of one hundred and twenty grains a day of it usually causes in man burning pain in the bladder and urethra, especially after urination, followed, if the dose be continued, by the appearance of albumin, red blood-corpuscles, and abundant renal epithelium in the urine. P. J. Cammidge has noted after the free exhibition of urotropin general formication, especially intense at night, ending in a few days in a diffuse rash, suggesting that of measles.

**Therapeutics.**—Hexamethylenamine was especially brought forward by Bardet and Laquers as a solvent for uric acid, but, according to the experiments of Arthur Nicolaier, it is less active in this respect than is piperazine, and is of no practical value for the solution of renal calculi. On the other hand, it ranks with piperazine as an alterative diuretic in the treatment of *pyelitis*, *cystitis*, and *ammoniacal phosphaturia*. In *gonorrhœa* it has failed to be of service.

Our present experimental knowledge so strongly confirms the clinical experience of Citron that in order to get the good effects of hexamethylenamine in genito-urinary inflammations it is essential to maintain the acidity of the urine, that in most cases benzoic or boric acid should be exhibited at the same time as is hexamethylenamine.\* Hexamethylenamine has been used as a prophylactic against nephritis in *scarlet fever*. Preisich found 9 per cent. of kidney lesions with urotropin as against 13 per cent. without. Dose, fifteen to twenty grains (1–1.3 Gm.) three or four times a day, well diluted.

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\* The clinical experiments of Suter seem worthy of note. He found after fifteen grains of phenyl salicylate, boric acid, or benzoic acid were exhibited to a healthy subject at bedtime, the early morning urine made as good a medium for the growth of bacteria as ordinary urine; but if forty-five grains of hexamethylenamine or of phenyl salicylate were given the urine passed was very inert towards bacteria; one to two days being required for the growth of bacteria in the salol urine, four days in the urotropin urine provided the urine was acid. Salol acted as well in the alkaline urine.

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## FAMILY V.—DIAPHORETICS.

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DIAPHORETICS are those medicines which are employed to increase the action of the skin. It is scarcely in place here to discuss the results of suppression of the functional activity of the skin or the importance of the surface-elimination to the system. It does seem well, however, to call attention to the fact that the perspiratory glands have a double function to perform,—that of elimination, already alluded to, and that of keeping down the temperature of the body during exposure to heat. When a man enters a Turkish bath the temperature of which is perhaps 160° F., or when he works in the sun on a very hot day, there is, if he be used to such exposure, little or no rise in the temperature of the body, because the surface-glands secrete sweat so actively as to expose a great amount for evaporation, and by the conversion of so much water into vapor such an amount of heat is absorbed—*i.e.*, converted from heat into repulsive force—that the body is cooled. The reason that even a moderate degree of heat in a moist atmosphere is intolerable is because evaporation cannot take place.

From what has already been stated, it is obvious that the use of dry external heat, or rather exposure to a hot atmosphere, is a powerful means of producing perspiration. It may be applied either in the form of the *Turkish bath*, in which the air of the hot chamber is very dry, or in the *Russian* or *vapor-bath*,\* in which the atmosphere is surcharged with hot vapor. Neither of these baths has any other physiological property than that of a sweat-producer.

*Hot-water baths* offer another very successful method of inducing profuse perspiration. The patient should be placed in a bath of about 100° F., and remain there from fifteen to twenty minutes, during which time, by the repeated addition of very hot water, the temperature should be raised to 110° F., or to such point as the patient can endure. Warmed blankets having been plentifully provided, the sick man should be lifted from the bath into them, be closely wrapped up, and so left for three or four hours before being transferred to the usual bed. According to A. Steffen, after this use of the bath the body has been proved to undergo loss of weight continuously for one or two days.

The popular belief that after a sweat there is a greater liability than usual to take cold appears to us to be well founded: care must,

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\* For home use there are in the market various "Cabinet Baths," so called, which afford a cheap and efficient means of giving vapor-baths. The term Turkish bath is here applied to the bath used in this country under that name. This bath appears not to be a copy of the Oriental bath, but merely a derivative from it. Writers affirm that in the East the sudarium, or sweating-chamber, rarely has a temperature of more than 98° F.: in London we have been in a Turkish bath at 200° F.: from 140° to 160° F. is a common temperature in American baths.



therefore, be exercised to avoid exposure after the hot bath of any kind. The liability to take cold may, however, be overcome by the use of the cold douche or plunge-bath.

The possibilities of the hot-water bath as a therapeutic measure are probably much greater than is ordinarily recognized. In severe *burns*, in *nervous shock*, and in various skin diseases continuous immersion would probably often be found of the greatest service. According to Baelz, the baths which are habitually taken by the entire native population of Japan are at a very high temperature (109° to 114° F.), and the immersion continuous during the whole evening. The mouth temperature rises to 104° or 105° F., while the pulse becomes very full and increased in frequency, with marked evidences of relaxation of the arteries. When there is a high grade of atheroma, the softening of the arteries after an hour's bath is very pronounced. Baelz believes that there is no increase in the elimination of nitrogenous matter, and that the Japanese custom is extremely useful, because, the winter being cold and the houses not heated, the people lose bodily heat during the day, and for two pennies in the evening acquire a supply of heat which lasts through the night.

Profuse sweating is always more or less exhausting, but is not nearly so much so as purging, and therefore may be practised in dropsical patients too feeble to allow of the use of purgatives. The hot baths are not, however, altogether free from danger or objection. Sometimes in the Turkish and Russian baths the patient fails to sweat freely, and a feeling of distress, a bounding, rapid pulse, and perhaps severe headache develop themselves: under these circumstances the bodily temperature rises, and a fever develops, which may go on to the production of a true "thermic fever," and perhaps terminate in sudden death. This is an exceedingly rare result, and one that can never occur if the patient is removed from the hot chamber so soon as any unpleasant symptoms are manifested. Sudden death has been recorded once from "sunstroke" in a patient while taking the "Turkish bath," also once from "congestion of the lungs."\*

According to Steffen, the hot-water baths are contraindicated by the existence of congestion or œdema of the lungs, or of a tendency towards these disorders. since under such circumstances the bath greatly increases the disease, or precipitates a perhaps fatal attack. Our own experience corroborates these statements. We have seen, under the conditions mentioned, the most frightful dyspnoea result from the use of the hot-water bath. If disturbance of the respiration comes on during the bath, the patient should immediately be taken out, and, if the symptoms be urgent, cold water should be freely dashed over the head, neck, and chest. Severe cardiac disease is also a contraindication both to the Turkish and Russian or vapor-bath.

Precisely as water may act as a diuretic by increasing the fluidity and amount of blood, so may it also act as a diaphoretic, provided

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\* *B. M. J.*, Oct. 1878.

that it is directed to the skin by being itself given warm and aided by the use of external heat; hence the importance of hot drinks when it is desired to produce free sweating. The colliquative "night-sweats" of phthisis are undoubtedly largely due to a paralytic weakening of the blood-vessels of the skin. In a similar manner aconite, veratrum, tartar emetic, and other substances which profoundly affect the circulation produce a free sweating which resembles that often seen in collapse from other than drug causes.

Diaphoretics are employed in the practice of medicine to fulfil the following indications:

First.—*To arrest forming diseases* of not very severe type, probably by causing a flow of blood to the surface, and thereby relieving slight internal congestions, and possibly by eliminating principles which have been retained in the blood instead of being excreted as they ought to have been. In *general cold*, in *muscular rheumatism*, in *suppressed menstruation*, and other results of exposure to cold and of checked perspiration, the diaphoretics afford the most efficient means at our command for restoring the normal functions.

Second.—*To favor absorption*. In *dropsy* the diaphoretics are of very great value, often aiding diuretics and purgatives in effecting a cure, and sometimes, when these fail, or when circumstances forbid their use, rescuing the patient from impending death. None of the medicinal diaphoretics except pilocarpine is of sufficient power to be relied upon in dropsy. The Turkish, the Russian, and the hot-water bath are capable of producing sufficient sweating to cause absorption of dropsical fluid, but must be vigorously employed.

Third.—*To aid in the subsidence of diseases* which naturally pass off with a sweat. The chief use of diaphoretics for this purpose is in *malarial fevers*, especially in the *remittent* form of the affection, when the sweating stage fails to develop itself thoroughly and the paroxysms run into one another. Even in the single paroxysm of *intermittent fever*, by hastening the closing stage, they often shorten the paroxysm.

Fourth.—*To eliminate noxious materials* from the blood. The old humoral idea that the groundwork of such diseases as fevers is a distinct *materies morbi* which can be eliminated from the blood has no sufficient demonstration to be accepted, and, although diaphoretics do good in *fevers*, yet it cannot be granted that it is in this manner. The very great power of increased diaphoresis in cooling the body through surface-evaporation has already been dwelt upon, and much of the good effected by diaphoretics in diseases of high temperature probably has its origin in this power.

Modern science seems clearly to point out that diaphoretics may aid in separating from the blood retained secretions, and may to some extent replace the action of the kidneys when these organs are disabled by disease.

In 1851 Schottin discovered urea in the sweat of patients suffering from the collapse of cholera. Not only has the discovery of Schottin been confirmed by the

researches of G. O. Rees, of Fiedler, of Hirschsprung, of Kaup and Jürgensen, of Leube, and of G. Deininger, but it has also been abundantly proved that the skin excretes urea freely during the advanced stages of Bright's disease, and also during the partial urinary suppression of scarlatinal desquamative nephritis. The urea in renal disease may even form a distinct crystalline powder on the skin, but it is most abundant about the mouths of the sweat-glands. We believe Landerer was the first to announce that urea is present in the sweat of healthy persons; and, although excellent chemists have been unable to detect it, its presence at times can no longer be denied, since it has been found not only by Landerer, but also by Funke in 1858, by Meissner, and by Leube; Fourcroy (quoted by Rees) has also found it in the sweat of horses. By a series of elaborate experiments, Leube has rendered it probable, if he has not actually proved, that in health there is such a relation between the skin and the kidneys that when the former is very active the latter excrete less than the normal amount of urea.

When to the facts already cited are added the observation of Griesinger, that in diabetes the perspiration contains sugar, and the well-known circumstances that in rheumatism the sweat contains lactic acid, and in jaundice biliary products, the value of diaphoretics as a means of getting rid of retained excretions becomes manifest. For this reason, in *Bright's disease*, especially of the acute form, they are of the greatest value, acting beneficially in three different ways,—by drawing the blood to the surface, and thereby relieving any internal congestions of the kidneys or other organs that may exist; by promoting the absorption of dropsical effusions; and by eliminating retained secretions.

The drugs which are used clinically for the purpose of increasing the sweating are spirit of nitrous ether, tincture of aconite, powder of ipecac and opium, and pilocarpine. The spirit of nitrous ether acts by dilating the vessels thus inducing, so to speak, an artificial congestion of the sweat glands. Although for this purpose ethyl nitrite is used almost exclusively, it is evident that any of the nitrites is capable of fulfilling the same indication.

It is probable that opium exercises a slight direct stimulant influence upon the sweat glands. Probably through the relaxing effects of nausea this action is greatly enhanced by ipecac so that the combination introduced by the famous pirate, Dr. Dover, has maintained its place as a practical diaphoretic for two centuries and still remains one of the most valuable combinations for the purpose of producing sweating.

### PILOCARPUS.

This drug, which has long been employed by the natives of South America,\* received its first notice, under the various names of *Jaborandi*, *Jaguarandy*, and *Jamguarandi*, from T. J. H. Langgaard in his *Diccionario de Medicina domestica*, Rio Janeiro, 1865. It attracted no attention, however, until 1874, when it was brought to Paris by Coutinho. The U. S. Pharmacopœia recognizes only the leaflets of

\* Under the name of Jaborandi various drugs other than the products of *Pilocarpus* are sold in Brazil. As the *Pilocarpus pinnatus* has been found to be active when grown in France, it is probable that the Jaborandi plant might be successfully cultivated in our Southern States. Frerichs (*Berlin, Klin. Wochenschrift*, 1875) found the wood inert.



two species, *Pilocarpus Jaborandi* and *Pilocarpus microphyllus*. These two shrubs are much alike, the leaflets of the compound leaves of the first variety are much larger than the second, being two to four inches long, while those of *P. microphyllus* are from one-half to one inch in length. Their activity is due to the alkaloid pilocarpine, discovered by Byarson.\* They should contain not less than 0.5 per cent. of total alkaloids.

#### Official Preparations :

Fluidextractum Pilocarpi.....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Pilocarpinae Hydrochloridum.....	$\frac{1}{2}$ to $\frac{1}{4}$ grain (0.005-0.015 Gm.).
Pilocarpinae Nitrates.....	$\frac{1}{2}$ to $\frac{1}{4}$ grain (0.005-0.015 Gm.).

**Physiological Action.**—*Local Action.*—*Absorption and Elimination.*—*Jaborandi* is practically free from irritant properties, and yields its active principle rapidly in the alimentary canal. After hypodermic injection of pilocarpine the symptoms may set in in five minutes. It is probable that the alkaloid escapes from both the skin and kidneys.

*General Effects.*—When an infusion of from sixty to ninety grains of *jaborandi* is given to an adult, in about ten minutes the face and neck become deeply flushed, and free perspiration and salivation commence. The sweating begins on the face; both it and the salivation are excessively profuse, and last from three to five hours. There is not rarely nausea, and sometimes vomiting. The pulse is usually more or less quickened, as is also frequently the respiration. After the sweating has ceased, the patient is left more or less exhausted. The nasal and lachrymal secretions are also very generally increased under the action of the drug, and Gubler has noted diarrhœa, which in the experiments of Ringer and others has not been present. There is sometimes contraction of the pupils, and even disturbance of vision. These effects of the drug are in the adult fairly constant; but subjects have been occasionally found who were not susceptible to the action of the remedy, and, very curiously, in Ringer's experiments children were found to be very insusceptible, although doses of sixty grains were employed. Schwann, Morat, and other observers have noticed in the lower animals that very violent gastric and intestinal movements are produced by the drug.

*Secretion.*—The dominant action of pilocarpine is to increase the secretory activity of all the glands of the body, especially those of the skin. The action is either on the secreting cells themselves or, as appears at present probable, on the peripheral nerve terminals within

\* Concerning the alkaloids of *jaborandi* and their derivatives there is much confusion and imperfection in our knowledge. Three alkaloids have been thought to exist in *jaborandi* leaves, namely, pilocarpine and its derivatives, *jaborine* and *pilocarpidine*. According to its discoverers, Harnack and Meyer (*A. E. P. P.*, xii.), *jaborine* acts upon the heart, pupil, intestines, and salivary glands in a manner almost identical with that of atropine, so that its occasional presence in commercial pilocarpine gives rise to vagaries of physiological and therapeutic action. Jowett, however, has been unable to isolate *jaborine*, and there is much doubt as to its being a constant constituent of *jaborandi*. (See Marshall, *B. M.*, 1900 ii.). Further, according to Marshall, *jaborine* sold by Merck is a mixture of pilocarpine and a fourth alkaloid, *isopilocarpine*. *Pilocarpidine*, according to Harnack (*A. E. P. P.*, xx.), causes in excessive dose violent sweating, salivation, also vomiting and purging, with great disturbances of circulation.

the glands. On account of the antagonism between the skin and the kidneys the diaphoretic dose of pilocarpine may cause a decrease in the urinary flow, but the assertion of Gubler that the alkaloid administered in very small repeated doses has a marked diuretic influence has received clinical confirmation.\*

The sweat produced by pilocarpine is often enormous in quantity (nine to fifteen ounces by estimation). Vulpian has shown that the sweat is, as normally, alkaline. In the analyses of Robin the chlorides were found in excess, the carbonates and phosphates in very minute amount, and the urea in more than five times its normal proportion, the amount eliminated in the sweating being estimated at from ten to fifteen grains. Hardy and Ball believed that in their experiments the average amount of urea eliminated by the skin was seventeen grains.

Jaborandi appears to have a stimulant influence upon secreting glands throughout the whole body. The nasal mucus is often greatly increased. The assertion of Pilicier, that in a dog with a gastric fistula the gastric juices were greatly increased by the drug, is in conformity with the free vomiting of large quantities of glairy secretion which it causes in man. Morat has noted a temporary increase of the sugar in the blood, an evidence that the glycogenic function of the liver is stimulated. The suprarenal capsules appear to share the action of the drug, since Auguste Pettit has noticed that in animals poisoned by jaborandi there is marked congestion and swelling of these bodies. According to Gottlieb, pilocarpine causes an increase of both the watery and solid constituents of the pancreatic secretion.

There appears to be some relation between the flow of saliva and that of perspiration produced by jaborandi: if the one is very profuse the other is often, but not always, correspondingly scanty. Sometimes the salivation almost replaces the sweating (Féréol); very frequently it commences before the sweating, and often it is more persistent. During it the mouth is warm, and there is often a feeling of tenseness about the maxillary glands. The saliva contains an abundance of salts and of ptyalin, as well as a small excess of urea. According to J. N. Langley, in the frog the mouth and skin, after the exhibition of jaborandi, become covered with a viscid secretion; in the dog, the rabbit, and the cat there is profuse salivation.

That the action of pilocarpine in increasing secretion is direct and upon the glands themselves is shown by the fact that the salivary glands are affected equally before and after section of all of the salivary nerves (Langley and Carville, confirmed by Schwann); also when the drug is injected directly into the gland and prevented from entering the general circulation (Langley). According to the elaborate experiments of Langley upon cats poisoned with pilocarpine, stimulation of the chorda tympani or of the sympathetic nerve causes respectively some increase or lessening of the secretion, but this increase or lessening is not nearly equal to that which occurs in the normal animal, and is due to the action of the nerves upon the circulation, and not to any influence on their secretory fibres. Very large doses of the drug injected into the gland immediately arrest the secretion, and doses of less size given in the same way, while increasing secretion, paralyze both chorda tympani and sympathetic nerve, so that stimulation of them has no effect. It is probable from the last fact that jaborandi has an action upon the secretory gland-cells.

There is evidence that the action of pilocarpine is on the intrinsic nerves rather than the glandular structures. Atropine will check the salivation produced by pilocarpine and it is probable that atropine acts on the nerve endings. Moreover

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\* Much interest attaches to the effect of jaborandi upon urea-elimination, but it cannot be considered as determined, except that in various diseases the combined renal and dermal elimination is greatly increased by the drug. Hardy and Ball state that in health urea-elimination from the kidneys is diminished by the drug, while Tyson and Bruen have found it increased both in health and in disease. The experiments have, however, been too few, and especially the conditions of their performance too lax, for much importance to be attached to them. As the result of experiments upon the lower animals, J. Horbaczewski (*Therap. Gaz.*, 1893) believes that there is a distinct relation between the elimination of uric acid and the number of leucocytes in the blood, and that pilocarpine in proper dose increases the size of the spleen and increases also the number of leucocytes in the blood and the quantity of uric acid eliminated.

Fuchsinger (confirmed by Nawrocki) has found that section of the nerves of the cat's leg did not prevent the paws from sweating when *jaborandi* was exhibited. But five or six days after the section, when the peripheral nerve-endings had undergone degeneration, Fuchsinger found that *jaborandi* was unable to excite sweating.

*Jaborandi* appears to stimulate the nutrition of the hair, and Prentiss, of Washington, has reported several cases in which the continued internal use of pilocarpine caused the hair to become exceedingly coarse and to change its color from light to dark. H. Rasori has noticed a tuberculated eruption apparently produced by *jaborandi*. M. Grocco has found that pilocarpine hypodermically injected or locally applied sensibly affects hysterical anesthesia.

*Circulation.*—Although very small doses of pilocarpine may produce an increase in the pulse rate, what is generally regarded as the characteristic effect in animals is a slowing of the pulse\* with a rise of the blood-pressure. According to Harnack and Meyer the rise of pressure is an indirect action of the drug; the slowing of the pulse is brought about by a stimulation of the peripheral endings of the pneumogastric nerve. After toxic doses the blood-pressure falls, due to vaso-motor paresis.

Although Harnack failed to obtain any evidence of primary increase in the pulse rate, the experiments of Kahler and Sayka, of Leyden, and of Reichert, demonstrate that if the dose is sufficiently small it does occur. The slowing of the pulse which occurs later is not prevented by previous section of the pneumogastric nerve but is at once set aside by an injection of atropine (Langley, Leyden, Harnack and Meyer), as is also the diastolic arrest of the heart which pilocarpine produces in the frog. Since Ringer has shown that this antagonism between pilocarpine and atropine holds true for the ventricular portion of the heart, and since the cardiac muscle retains its normal irritability it follows that the action of the drug must be upon the nerve terminals within the heart muscle.

The rise of the arterial pressure is stated by Harnack and Meyer to be prevented by the use of curare and artificial respiration, and to be, therefore, a secondary, not a direct, result of the drug's action: it is probably due to the convulsive muscular contractions produced by the drug. In the latter stage of the poisoning the arterial pressure falls. As in the experiments of Harnack and Meyer asphyxia in this stage did not cause rise of pressure, although the heart appeared still to retain its force, the vaso-motor system is probably paralyzed, a conclusion confirmed by the later experiments of Reichert. The pulse still continues slow, although, according to Harnack, the vagi are completely paralyzed.

*Respiration.*—According to the experiments of Morat and Doyon, pilocarpine produces a distinct slowness of the respiration, and as a respiratory poison is the antagonist to atropine.†

*Sexual Organs.*—*Jaborandi* does not appear to have any power over the sexual organs, except the pregnant womb. Cases of abortion during its use have been reported by Masmann (quoted by Larvand) and by Schanta, but in the hands of other observers the drug has appeared to have little, if any, abortifacient influence, and Hyernaux

\* The therapeutic dose generally produces in the human being quickening rather than retardation of the pulse.

† H. Dreser (*Arch. f. Exper. Path. u. Pharm.*, 1892, xxx.) has experimentally found that pilocarpine markedly increases the oxygen in the air of the swimming bladder of the carp.



and Chanteril have found it powerless in the lower animals (quoted by Larvand). When, however, the pregnant female is at her full term, the drug may affect the uterine contractions, as Larvand and others have noted an increase of the pains, or even a precipitation of labor, both in women and in the lower animals. Nevertheless, the oxytocic powers of jaborandi are very feeble.\*

*Motor System.*—In man, muscular tremblings have been observed during the action of jaborandi, but it is doubtful whether they are due to a direct action of the remedy. In the frog, as first noticed by Murrell, small doses (three milligrammes of pilocarpine) produce violent convulsions with heightened reflex activity, while larger amounts cause complete palsy. According to Harnack and Meyer, the convulsions are due to spinal stimulation, and the paralysis partly to overwhelming of the spinal centres and partly to paralysis of the muscles, the motor nerves themselves not being affected. The action of the drug upon the musculo-nervous system is entirely subservient to its other effects.

*Eye.*—When applied to the eye, pilocarpine produces contraction of the pupil, tension of the accommodative apparatus, and an approximation of the near and far points of distinct vision.† Tweedy also states that there is impairment of vision, due to benumbing of the retina. According to P. Albertoni, the myosis is followed by a moderate but persistent mydriasis, and is not prevented by previous section of the oculo-motor nerve or of the upper cervical sympathetic ganglion. It is certainly the result of a peripheral influence. Galezowski, who uses a solution of one part of a pilocarpine salt in fifty of water, affirms that it answers as well as a solution of eserine in diseases of the eye, and has the great advantage of not producing irritation.

*Temperature.*—Robin affirms that before and during the early stages of the sweating from jaborandi the temperature rises 1° to 2° F., but afterwards falls as much below the normal point and remains depressed for one or two days. This primary rise of temperature has been noted by other observers,‡ but is frequently absent altogether or very trifling.§ The subsequent fall of temperature, which is a constant phenomenon, probably depends in great part, or altogether, upon the loss of heat during the sweating.

*Nutrition.*—The interesting question whether the excessive secretion of solids from the skin and urine produced by pilocarpine is accompanied by any increase of waste products in the body, or is only due to an increased activity of the glands in clearing out waste products already produced, cannot at this time be answered. According to Otto Frank and Fritz Voit, the first dose of the alkaloid

\* See *British Medical Journal*, 1879, ii. 509; also *Wien. Med. Blätt.*, 1879, ii. 1178, 1207.

† See John Tweedy (*Lancet*, 1875, i. 159), C. Scotti (*Berl. Klin. Wochens.*, 1877, 143), and Galezowski (*Med. Times and Gaz.*, 1877, ii. 358).

‡ See Ringer (*Lancet*, 1873, i. 157), Greene (*Phila. Med. Times*, vi. 56), Scotti (*Berlin. Klin. Wochens.*, 1877, 141), Pilicier (*Med. Centralbl.*, 1876, 429), and Weber (*Ibid.*, 770). Pilicier noted that the rise occurred in the axilla, but not in the rectum: this would indicate that it is a local phenomenon, the result of a heating of the surface, not of the interior, of the body.

§ Consult Riegel (*Berlin. Klin. Wochens.*, 1875, 86), Bardenhewer (*Ibid.*, 1877, 8), and Autschmann (*Ibid.*, 353).

causes in the curarized dog increased elimination of carbonic acid, but a second dose, given when the carbonic acid elimination has returned to the normal, has no such effect; it is therefore probable that the drug has no direct influence upon nutrition.

**Therapeutics.**—Jaborandi is by far the most reliable and powerful remedy of its class, and is always selected when it is desired to produce a very active sweating, as in *uremia* or in *dropsy*. Both in *acute* and *chronic Bright's disease* it is of very great value, either as an aid to or as a succedaneum for the vapor-baths. The sweating should be repeated at regular intervals, varying from one a day to one a week, according to the nature of the case.

Not only is jaborandi valuable for the removal of distinctly excrementitious material from the blood, but it is often of the greatest service in arresting the development of a forming disease, probably by eliminating peccant matters. Thus, in the onset of an attack of *influenza*, in the beginning of a *bilious fever*, and in *subacute* and *muscular rheumatism* it may often be used with great advantage. On the other hand, when in a fever it is desired not to produce a single excessive sweating, but simply to maintain moisture of the skin, jaborandi will hardly serve the purpose of the practitioner, and in *typhoid* or other asthenic fevers more or less danger of exhaustion attends its use.

In doses of from one-twelfth to one-fifteenth of a grain (0.005–0.004 Gm.), given every two to four hours, pilocarpine usually causes a decided increase in the secretion of urine, and is a valuable remedy in the treatment of *cardiac* and of *renal dropsies*. In rare cases albuminuria and even strangury\* have followed this use of the drug, so that some caution would seem to be necessary in its employment in the early stages of *acute nephritis*. Nevertheless, we have seen it apparently successful in *acute suppression of urine*.

In the treatment of *pseudo-membranous laryngitis* and in *diphtheria* pilocarpine was at one time extensively used, under the belief that by increasing the secretion beneath the membranes it would loosen them; it has, however, failed to establish its value for this purpose. Ringer has reported several cases of *unilateral sweating* cured by the use of full doses of pilocarpine given hypodermically. It has been used with asserted success in *alopecia*. Cheron affirms that, when given in doses of one-twelfth of a grain hypodermically, pilocarpine is very effective as a galactagogue, but Cornevin found that in cows, at least, pilocarpine has no influence upon the quantity of milk secreted, though it increases the production of lactose.

Locally applied (half-ounce of the leaves) in the form of a poultice, jaborandi may sometimes produce local sweating only, but we have seen marked and extraordinarily prolonged general sweating so caused.

**Ophthalmic Uses.**†—The instillation of a one-per-cent. solution of pilocarpine hydrochloride into the eye is followed by exactly the

\* See Purjesz (*Deutsch. Arch. f. Klin. Med.*, xvii, 533); also Stumpf (*Deutsch. Arch.*, xvi.).

† This section was written by Professor George E. de Schweinitz.

same results as those which have been described in connection with eserine. Pilocarpine fulfils all the therapeutic indications of eserine. It is not, however, as active, and therefore the strength of the solution used must be greater. It has the advantage of being less irritating and less liable to cause iritis.

**Administration.**—Pilocarpine frequently causes much nausea and even vomiting, and we have found that when it is desirable to produce an excessive sweating for the purpose of breaking up a forming disease, much better results may be obtained by conforming to the following procedure than by giving pilocarpine unaided: let the patient, prepared for bed, take one dessertspoonful of a mixture containing, to the dessertspoonful, one-twelfth of a grain (0.005 Gm.) of pilocarpine hydrochloride, five grains (0.3 Gm.) of antipyrine, and three to ten minims (0.06–0.2 C.c.) of tincture of aconite-root; soak the feet fifteen minutes in a hot mustard bath; on getting into bed take a teaspoonful of the pilocarpine mixture, with a tumbler of very hot lemonade or whisky punch; repeating every twenty minutes the pilocarpine mixture until free perspiration sets in.

**Antagonism with Atropine.**—In 1875 Langley called attention to the antagonism existing between jaborandi and belladonna. When the heart has been slowed or arrested by jaborandi, atropine will bring the rate of pulsation almost to normal; the reverse of this also occurs, provided the amount of atropine previously applied has not been too great (Langley). Upon the sweat-glands the two drugs have also antagonistic powers, one being able to annul the action of the other (Fuchsinger). The same is true in regard to the salivary secretion (Langley). This antagonism between atropine and jaborandi is affirmed by H. Larvand to extend to the intestines and pupil. In belladonna-poisoning the alkaloid has been used with no advantage in very small dose, but in a case in which nine-tenths of a grain of atropine had been taken, nine grains of pilocarpine are said to have been injected hypodermically in between one and two hours with success (Purjesz). L. Juhász reports a case in which it was estimated that about one and a half grains of atropine were taken, followed in half an hour by vomiting; four and a half grains of pilocarpine were injected in about seven hours, with a favorable result. Hofferts reports a case in which seven and a half grains of extract of belladonna were ingested, and nearly two grains of pilocarpine given, with recovery.\*

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## FAMILY VI.—EXPECTORANTS.

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UNDER the present heading we propose to discuss not only true expectorants,—that is, those medicines which have the power of influencing diseased conditions of the respiratory mucous membranes,—but also various substances and even various procedures which are employed for the relief of pulmonic conditions.

*Cough.*—When from disease, or from other causes obnoxious materials, be they secretions or foreign matters, accumulate in the bronchial tubes, cough is necessary for their expulsion, so that in a large proportion of cases no treatment of cough is desirable. On the other hand, there are cases in which, owing to excessive irritability of the pulmonic mucous membrane, the amount of cough is out of all proportion to the amount of material to be expelled. Under these circumstances the symptom is not only annoying, but also, by irritating the mucous membrane of the lungs and by exhausting the patient, directly harmful. In another set of cases, owing to muscular weakness and to lack of irritability of the mucous membrane, the cough is not sufficient for the expelling of the secretions, which gradually accumulate in the lungs, fill up the bronchial tubes, and finally, it may be, cause death by a process comparable to that of drowning.

It is plain that the medical practitioner must study in each individual case the relations between the cough and the amount of work required; so that if the cough be excessive it may be allayed, if it be insufficient it may be stimulated. For the purpose of allaying cough, soothing vapors or liquids may be applied to the respiratory mucous membrane by inhalations, but in the majority of cases internal anodynes are necessary.

In some instances the cough is maintained by an excessive irritability in the upper throat and air-passages, so that demulcents such as liquorice are very useful, or relief may be obtained by sipping a mixture composed of glycerin and whisky, each one part, with two to four parts of water.

The anodyne substances which are employed for the relief of cough are hydrocyanic acid, belladonna, hyoscyamus, chloroform, the bromides, morphine, codeine, and heroine. The action of hydrocyanic acid is too brief for the remedy to be of practical value. Belladonna, unless locally applied by means of atomization, is very uncertain in its action and of entirely secondary importance; superior to it is hyoscyamus, although even full doses of this remedy often are ineffective. Chloroform, in doses of ten to fifteen minims (0.6–0.9 C.c.), sometimes acts most happily, but must be given at very

short intervals on account of the fugaciousness of its influence, and is more useful in combination than alone. The bromides in full doses are often effective, and may well be combined with chloroform; in some cases they are too depressant. Much more certain in its influence than any remedy yet mentioned is opium; its tendency to check secretion forbids its use, however, in a very large proportion of cases, notably in those in which there is persistent dryness of the bronchial mucous membrane, whether this dryness represents the first stage of an acute bronchitis or whether the case be one of a continuing subacute bronchial irritation so frequent in neurotic individuals. Moreover, the usefulness of opiates is further limited by their tendency to derange digestion, and in chronic cases by the danger of forming the opium habit. Under these circumstances the diacetyl ester of morphine (heroin) is very valuable.

We know of no method of increasing the irritability of the pulmonary mucous membrane when impaired. In such cases, if the loss of irritability be, as it usually is, dependent on general atony, strychnine and cocaine may be administered in full doses, and are sometimes very serviceable. In an acute case, with failure to expel the secretion, as in the *suffocative catarrh* of infants, life may sometimes be saved by mechanical treatment. Stimulating emetics are often of the greatest service in freeing the bronchial tubes of secretion. On various occasions we have resuscitated young children after they had become completely comatose and lost the ability of swallowing from asphyxia due to suffocative catarrh, by the following procedure, which was suggested to us by the well-known reflex spasmodic contraction of the respiratory muscles produced by a dash of cold water on the chest:

Provide three tubs, one empty, one containing ice-water, and one with water at about 115° F. Hold the naked body of the child over the empty tub, and dash over the upper thorax a ladleful of the hot water, followed immediately by one of the cold water. So soon as the color of the skin has begun to change under the respiratory gaspings, and some evidences of consciousness appear, dip the body of the child momentarily in the hot water, when the scream produced by the pain will usually fill the lungs with air. In this procedure the hot water is used alternately with the cold water to prevent chilling of the body as well as to increase the shock.

*To allay Spasm.*—When a spasm affects the laryngeal muscles acutely it may often be put an end to by an emetic dose of ipecacuanha or, in a very robust subject, of lobelia; but in some cases, especially in so-called *laryngismus stridulus*, the exhibition of an anesthetic may be necessary for the saving of life. In such cases chloroform should be selected on account of the locally irritating influence of ether. Amyl nitrite in alarming cases often acts most happily. For the prevention of the recurrence of these spasms the various anodynes mentioned above may be employed. The most generally successful is the bromide, which in *spasmodic croup* should be given repeatedly in full doses. Local applications of belladonna—the smoking of belladonna cigarettes—are often very useful.



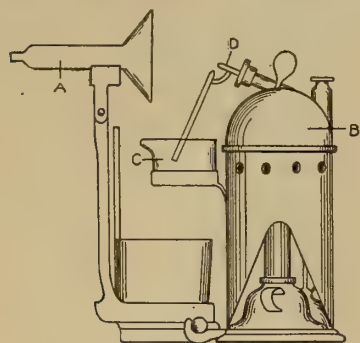
In extreme cases of asthmatic bronchial spasm relaxation may be obtained by the exhibition, in robust cases, of lobelia in full doses, by smoking belladonna or stramonium cigarettes or pipes,\* by the inhalation of amyl nitrite or chloroform, or by hypodermic injections of morphine or of heroine hydrochlorate.

Local applications may be made to the lungs in the form of vapor or of fine spray obtained by the so-called pulverization of water.

Atomization consists in breaking up by a mechanical contrivance solutions of a medicinal substance into a fine spray. At one time it was believed that in this way the finest ramifications of the bronchial tubes could be reached, but the method has gradually passed out of use except for cases in which the disease is in the fauces, larynx,

or trachea. In using atomization it must be remembered that it is only a means of making a local application to a certain part, so that the rules governing the choice of drugs to be employed are precisely those affecting local applications to other than the respiratory mucous membrane.

By atomization warm water may be applied as a diluent and as a soothing application, its soothing properties being capable of increase by the addition of cocaine, opiates, or other narcotic remedies. By atomization stimulant substances, such as ammonium chloride, also benzoates, carbonates, or other antiseptics, may be brought in contact with a diseased mucous membrane. When there is



STEAM ATOMIZER.

FIG. 19.—When steam is generated in boiler B, passing out through tube D, it draws up any medicament which may be placed in cup C; the mingled warm aqueous vapors and drug are inhaled by the patient through A. The mode of treatment is of especial value in acute laryngitis and bronchitis.

excessive secretion, as in *bronchorrhœa*, or hemorrhage, as in *hemoptysis*, the practitioner may use in the atomizer such astringents and hemostatics as—tannic acid, one to twenty grains to the fluidounce; alum, from five grains to the fluidounce to a saturated solution; iron, Monsel's solution, five to fifteen minims to the fluidounce. In all cases in which strong local applications are being made to the lungs the occurrence of severe cough is an indication that the application is causing much irritation.

For purposes of study the expectorants may be divided into two groups; (1) those which tend towards relaxation in the bronchial

\* There are upon the markets numerous proprietary mixtures for the relief of *asthma* by smoking; most if not all of them consist of powdered belladonna or stramonium, mixed with potassium nitrate and sometimes other substances. Clinical experience has shown that the efficiency of these powders is increased by the presence of arsenic, which probably acts by stimulating the bronchial mucous membrane to secrete freely. The following formula, taken from an old *Pharmacopœia* of the Philadelphia Hospital, we have found to yield a very efficacious paper.

CHARTA ARSENICALIS COMPOSITA (Compound Arsenical Paper). R—Belladonnæ fol., gr. xvi; Hyoscyami fol., Stramonii fol., aa gr. xlviii; Extr. opii, gr. iv; Tabaci, gr. lxxx; Aquæ, Oj; M., ft. sol. et add. Potas. nit., gr. clx; Potas. arsenit., gr. ccxx. Saturate bibulous paper and dry for use. Roll the paper into cigarettes, one of which is to be smoked two to six times a day until relief is afforded or some giddiness is produced.

blood-vessels and increase of secretion, the so-called sedative or nauseating expectorants; (2) those which tend to overcome vascular relaxation and to diminish bronchial secretion. The first group are to be chosen in the early stages of an acute bronchitis, before secretion is established, while the "cough is tight;" the second group are more useful in chronic bronchitis or in the advanced stages of an acute condition.

Of course, it must be understood that the division which has been made is arbitrary, and that very frequently there are conditions in which expectorants of one group may well be combined in one prescription with those of another group. Thus, ipecacuanha and ammonium chloride are often very serviceable in union.

### NAUSEATING EXPECTORANTS.

One of the effects of nausea is an increase in the bronchial secretions; consequently any nauseating emetic acts, when given in smaller dose, as an expectorant. Those which are used practically in the first stages of a bronchitis are lobelia, antimony and potassium tartrate, ipecacuanha, potassium citrate, and apomorphine.

Of these substances *Lobelia* is to be employed only in asthmatic cases in which there is distinct tendency to spasm of the bronchial tubes. The tincture may be given in doses of fifteen to twenty minims (1-1.3 C.c.) every three hours, or when a spasm amounts to a violent *asthma*, one fluidrachm (4 C.c.) may be exhibited every two hours until vomiting is produced. When large doses of lobelia are given the patient must be closely watched, as sometimes an alarming depression is produced.

*Antimony and Potassium Tartrate* is similar in its expectorant influence to ipecacuanha, but much more powerful and much less safe. It should never be used in adynamic cases or with young children. Dose, as an expectorant, one-twelfth to one-sixth of a grain (0.005-0.01 Gm.), repeated according to circumstances.

*Ipecacuanha* is very largely used in the early stages of *acute bronchitis*, and is the safest of the nauseating expectorants. The dose of the syrup is from one-half to one fluidrachm (2-4 C.c.) every two to four hours, according to the exigencies of the case.

*Apomorphine Hydrochloride* is a valuable sedative expectorant, useful in exactly the class of cases in which ipecacuanha is commonly given.

*Potassium Citrate*, when given in large doses, perhaps because of its alkalizing effects, has a very notable effect in diminishing the viscosity and tenacity of the bronchial secretion during the dry stage of a *bronchitis*, and especially lends itself under these circumstances to combination with ipecacuanha, or in very robust cases with tartar emetic; one ounce (30 Gm.) of it should be given in the twenty-four hours. For many patients its taste is well concealed by lemon-juice.

**SAPONIN.**—The saponins are a group of glucosides more or less closely related both chemically and physiologically. Their name originated from their property of emulsifying fats and hence acting as cleansing agents. Some of them are highly toxic (these are called sapotoxins) while others are only feebly so.

These glucosides are very widely spread throughout the vegetable kingdom, Kobert giving a list of one hundred and forty plants which contain principles of the saponin class. According to the same authority, chemically pure saponin is physiologically inert, but saponin of commerce is a very active poison, and all of the plants containing it in considerable amount are capable of producing symptoms similar to those caused by commercial saponin. The symptoms caused by poisoning with saponin plants are violent vomiting and purging, the result of an intense gastro-irritation; convulsions; renal irritation; alterations in the blood itself,—these plants being, in fact, actively toxic to all forms of protoplasm.

On account of the irritant action of saponin on the stomach plants containing it reflexly increase the bronchial secretion, acting therefore as nauseating expectorants.

Two drugs containing saponin in considerable quantity are recognized by the U. S. Pharmacopœia, and, to some extent, used in practical medicine,—senega and quillaja.

#### Official Preparations:

Fluidextractum Senegæ.....	10 to 15 minims (0.6–1 C.c.).
Syrupus Senegæ (20 per cent.).....	1 fluidrachm (4 C.c.).
Fluidextractum Quillajæ.....	3 to 5 minims (0.2–0.3 C.c.).
Tinctura Quillajæ (20 per cent.) .....	15 minims (1 C.c.).

*Senega* is the root of the indigenous *Polygala Senega*. It is used to a considerable extent in the United States as a stimulating expectorant in the very advanced stages of acute *bronchitis* with free expectoration. It is really of little value, and causes in full dose much gastro-intestinal irritation.

*Quillaja* or *Soap-bark*, the inner bark of the Chilean tree, *Quillaja Saponaria*, is probably the most actively poisonous of all the saponin-containing drugs. On account of its detergent properties, it is very largely used in the arts for cleansing silk and other fabrics. It is also employed as an emulsifying agent by the apothecaries, but its active physiological properties forbid such use of it. Kobert recommends it as a cheap substitute for senega, given to the adult as a stimulating expectorant, a tablespoonful of a two- and a half-per-cent. decoction.

#### STIMULATING EXPECTORANTS.

The so-called stimulating expectorants are more or less volatile irritating substances, which are partially eliminated by the lung and exercise a stimulant action on the bronchial mucous membrane during their excretion. Creosote, oil of eucalyptus, oil of turpentine,



and oil of sandal wood, which are important members of the group, are considered elsewhere in this treatise.

**TERPIN HYDRATE.**—(*Terpini Hydras.*)—This derivative of oil of turpentine results from the action of nitric acid and water upon the oil of turpentine; the presence of alcohol facilitates its formation. It occurs in colorless, nearly odorless prisms, of a slightly aromatic and somewhat bitter taste, nearly insoluble in water, soluble in alcohol. Terpin Hydrate is used in practical medicine as a stimulant expectorant, resembling in its action other members of the turpentine group, and is especially useful in the advanced stages of *acute bronchitis* when the secretion is unusually free. In our experience it is better borne by the stomach than is terebene, and is, in its action upon the lungs, scarcely distinguishable from that agent. It has also been used in chronic *cystitis*, and in *gonorrhæa*. It may be given in doses of from three to six grains (0.2–0.4 Gm.) four to six times a day, in capsules.

**TEREBENE** (*Terebenum*) is a clear, colorless liquid, almost insoluble in water, isomeric with turpentine, and of a peculiar odor, somewhat resembling that of freshly sawed pine wood. It is prepared by the action of sulphuric acid upon oil of turpentine.

Terebene, one of the most effective of the stimulant expectorants, was first recommended by William Murrell. It is very useful not only in *chronic bronchitis*, but also in the *acute* disease after the earlier stages have passed by. As an expectorant it is nearly equivalent to the oil of eucalyptus, but is more stimulating. It has also been employed with asserted good results in *dyspepsia*, especially in the flatulent intestinal variety, and may be used in chronic or subacute *inflammations of the genito-urinary tract*. Its action upon the general system has not been investigated, but probably resembles that of oil of turpentine. From twenty to forty minims (1.3–2.5 C.c.) of it may be given to the adult in the course of twenty-four hours. It lends itself well to use by inhalations, either by atomization of water containing it or by vaporization from hot water. The vapor should be as concentrated as can be borne without exciting cough.

**TAR** (*Pix Liquida*) is a black semi-liquid substance, of peculiar odor and taste, obtained by the destructive distillation of various species of pine. The tar used in this country is almost exclusively the product of the *Pinus palustris* of North Carolina and other of the Southern States. In composition it is very complex. When distilled, it yields an oily liquid, known as *oil of tar*, *pyroligneous acid*, and a solid, black residue, *pitch*. It is freely miscible with alcohol, ether, and the fixed and volatile oils, and also to a slight extent in water.

The virtues of tar undoubtedly reside chiefly in the oil. This is a complex body containing creosote, phenol, and several allied compounds besides toluene, xylene and other bodies of minor impor-

tance. According to Taylor, the *oil of tar* has produced death in man. To cause death, tar itself would have to be ingested in enormous quantity, since a sailor (according to Stillé) recovered after taking between a pint and a quart of it.

#### Official Preparations :

Oleum Picis Liquidæ.....	3 to 5 minims (0.2-0.3 C.c.).
Syrupus Picis Liquidæ (5 per cent.).....	1 to 2 fluidrachms (4-8 C.c.).
Unguentum Picis Liquidæ (50 per cent.).....	External use.

Tar is used internally solely in the advanced stages of obstinate *acute bronchitis*, or in *chronic bronchitis*. Locally, it is much employed in *chronic diseases of the skin*, as a stimulant antiseptic application in the form of the official ointment. In many cases this is too severe, and the strength must be reduced. Hebra states that if it be applied too freely enough of the tar may be absorbed to darken the color of the feces and the urine, and even to cause gastric irritation and black vomit. For internal administration the most elegant preparation is the *Syrup of Tar*.

**GRINDELIA.**—This is the leaves and flowering tops of *Grindelia robusta* and of *Grindelia squarrosa*, plants inhabiting the extreme western portions of North America. In commerce the whole herb, including the stems, roots, and floral heads, is sold. The taste is warmish, peculiar, and very persistent. The presence of a crystalline alkaloid in *grindelia* has been asserted by several investigators, but at present it seems probable that its activity depends upon a turpentine-like volatile oil.

Fluidextractum Grindeliæ.....	30 to 60 minims (2-4 C.c.).
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**Physiological Action.**—The toxic powers of *grindelia* are said to be so feeble that three drachms of the fluidextract are required to kill a rabbit. According to Buffington, it produces narcosis with dilated pupils by a cerebral influence, but acts more powerfully in paralyzing the nerves of sensation and the sensory side of the cord, and finally attacks both the motor cord and nerves. Buffington also affirms that it causes in warm-blooded animals a slowing of the action of the heart by stimulating the inhibitory apparatus, and an elevation of the blood-pressure by stimulating the vaso-motor centres. Dobroklowski states that the large but non-toxic doses increase the pulse-rate as well as the arterial tension by a direct influence upon the heart or the peripheral vessels; that in toxic dose the drug depresses the pulse-rate and the arterial tension, and finally arrests the heart in diastole.

**Therapeutics.**—*Grindelia* has not been employed for its effect upon the circulation, and in the doses used in medicine it appears to exert no distinct influence upon the heart or arteries. It has been largely used, often with alleged excellent results, in *asthma*, and in *bronchitis* associated with a tendency to bronchial spasm. It is prob-

able that in these cases it not only has a relaxing influence, but also stimulates the mucous membrane, and even in *chronic bronchitis*, especially of the aged, it is said to do good. It has been employed in *whooping-cough*. Its active principles are probably excreted by the kidneys; hence after large doses there are sometimes evidences of renal irritation, and in *chronic catarrh of the bladder* good has been effected by its stimulant influence upon the mucous membranes of the viscus. It has also been employed as a local application, with alleged good results, in *vaginitis*. The fumes of burning grindelia are sometimes inhaled with alleged relief in *asthma*. The plant should be steeped in a solution of nitre, dried, and burnt upon a plate, or may be smoked in cigarettes or in a pipe.

**BALSAM OF PERU** (*Balsamum Peruvianum*) is obtained from *Toluifera Pereira*, a tree of Central America. This balsam is a viscid, honey-like, fragrant, brownish fluid, of a warm, bitterish taste, which has been shown by Bräutigam and Nowack to be practically devoid of antiseptic properties. According to Frémy, it contains not benzoic, but cinnamic acid. It has been used in *chronic catarrhs* of the respiratory and genito-urinary systems; dose, half a fluidrachm (2 C.c.).

**BALSAM OF TOLU** (*Balsamum Tolutanum*) is obtained from *Toluiifera Balsamum*, a tree very closely allied to that which yields the balsam of Peru. Balsam of Tolu is at first a thick, plastic solid, but by time it is converted into a hard, translucent, resinous solid. Its odor is highly fragrant and its taste vanilla-like. It contains cinnamic acid and a volatile oil, and its medical properties are the same as those of the balsam of Peru. On account, however, of its grateful taste, it is preferred to the latter, and is very much used to flavor medicines, especially cough-mixtures. In full dose, every three hours, it may be of some value in *chronic bronchitis*, but as generally used its preparations are simply agreeable vehicles.

#### Official Preparations:

Balsamum Tolutanum.....	15 to 30 grains (1-2 Gm.).
Tinctura Tolutana (20 per cent.).....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Syrupus Tolutanus (1 per cent.).....	$\frac{1}{2}$ to 1 fluidounce (15-30 C.c.).

There are a number of expectorants of very small value, but requiring notice on account of their being in use. *Ammoniac* (AMMONIACUM), an irritant gum-resin, was formerly used to a considerable extent in *chronic bronchitis* in doses of from twenty to thirty grains (1.3-2 Gm.); of the emulsion (EMULSUM AMMONIACI—four per cent.), one to two tablespoonfuls may be given. *Horehound* (MARRUBIUM, U. S.) contains a volatile oil and a bitter principle, *marrubiin*; also tannin. It is used domestically to a considerable extent in catarrhs of the upper respiratory tract. Dose of the powder, thirty grains to one drachm (2-4 Gm.). *Bloodroot* (SANGUINARIA, U. S.) is in overdoses an emetocathartic and narcotic poison. It contains sanguinarine and other alkaloids, and has been used in *chronic bronchitis*, but has no practical value. Dose of the fluidextract (FLUIDEXTRACTUM SANGUINARIÆ, U. S.), two minims (0.1 C.c.). Sanguinarine is a violent poison, causing in mammals vomiting, purging, collapse, convulsions, loss of reflex activity, cardiac depression, and finally death from asphyxia. (For details see eleventh edition of this treatise.)



**SULPHURETTED HYDROGEN.**—In 1886 Bergeon proposed a method of treating *phthisis* by filling the large intestine with sulphuretted hydrogen diluted with pure carbonic acid gas. After an extraordinary but very brief popularity the method has fallen into such complete desuetude that it is only necessary here to refer to the tenth edition of this treatise for details.

Sulphuretted hydrogen is, however, a valuable remedy in the treatment of purulent *pulmonic catarrhs*, whether of tubercular or other origin. When, under any circumstances, a bronchial catarrh is accompanied by very free expectoration the remedy may be useful in relieving the mucous membrane. We have also found it of service in *chronic gout*, when administered persistently for months. The method of administration employed by Bergeon was barbarous and absurd. The sulphuretted hydrogen may be given by the mouth in the form of a natural sulphur-water or, better, by means of water saturated with sulphuretted hydrogen and carbonic acid gas. The dose of the saturated solution is two to four ounces (60–120 C.c.), three or four times a day. In some cases it produces digestive disturbance, and its use has to be abandoned. That the gas is absorbed and eliminated by the lungs is proved by the very perceptible odor upon the breath. Many of the sulphur springs of Europe have inhaling chambers, and experience has shown that the sulphurous vapors are of value.

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## FAMILY VII.—EMMENAGOGUES.

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EMMENAGOGUES are medicines which are employed to promote the menstrual flux. In the great majority of cases amenorrhœa is merely a symptom of some constitutional disorder, as chlorosis, or tuberculosis, and is to be regarded rather as a conservative symptom than one to be relieved, and, therefore, the emmenagogues have largely gone out of use. In some instances, however, it is possible that the menses may be checked as a result of some nervous influence and re-establishment be desirable. The drugs which are used for this purpose are mostly remedies which are local irritants and are supposed to act by stimulating the uterine mucous membranes. Cantharides and guaiac, which are sometimes used for this purpose, are considered in other portions of this book.

SAVIN.—The dried tops of *Juniperus Sabina*, a juniper, native of the south of Europe and the Levant, contain a turpentine-like volatile oil. This oil is a powerful irritant. When taken in sufficient dose, it produces severe abdominal pain; incessant vomiting and bloody purging; diminution or even suppression of the urine, which is often albuminous and bloody; disordered respiration; symptoms of disturbed innervation, such as unconsciousness, stertorous breathing, and convulsions or convulsive tremblings; the scene closing by death in collapse. In pregnant females, abortion, accompanied by violent flooding, almost always occurs before the fatal issue. After death, signs of gastro-intestinal inflammation are generally present, but in some instances these are wanting, and in one case reported by Letheby pulmonary apoplexy and congestion of the brain were the chief lesions.

### Official Preparations :

Oleum Sabinæ.....3 to 5 minims (0.2–0.3 C.c.).

Fluidextractum Sabinæ.....10 to 20 minims (0.6–1.2 C.c.).

Although in rare cases of *menorrhagia* dependent upon uterine relaxation, the oil of savin is useful, its importance is chiefly owing to the frequency of its domestic use as an abortifacient,—a use which is accompanied by the gravest danger to life and has often ended in death.

RUE.—The leaves of *Ruta graveolens*, or common garden rue, contain a volatile oil whose properties are similar to those of oil of savin. It has been used in Europe for the production of criminal abortion, but seems to be less employed than is the oil of savin, and to be less dangerous, as we have met with no records of death from it except that of a man weakened by dysentery.\* According to M. Hélie, taken

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\* Case of G. F. Cooper (*Med. Examiner*, N. S., ix. 720).

internally, in large doses, it causes violent gastric pains, excessive and sometimes bloody vomiting, profuse salivation and swelling of the tongue, great prostration, confusion of mind, and convulsive twitchings, with, in pregnant women, abortion.

**TANACETUM.**—The common tansy of the gardens, *Tanacetum vulgare*, in the form of decoction, or of its volatile oil, is sometimes used as a stimulant emmenagogue or for the purpose of producing abortion, but is a very unsafe remedy. When taken in sufficient amount it causes abdominal pain, vomiting, loss of consciousness, and violent epileptiform convulsions.\* The minimum fatal dose of the oil of tansy is not known, but in two cases a teaspoonful of the oil produced violent epileptiform convulsions, and the same amount is said to have caused death. Recovery is stated to have occurred after two teaspoonfuls (Whitehill); also after three fluidrachms. The action of the oil upon the lower animals has been studied by Guillery. In frogs the most important effects which it was found to produce were paralysis of the peripheral endings of the motor nerves, with early appearance of post-mortem rigidity; and paralysis of the vaso-motor centre of the medulla and of the inhibitory cardiac apparatus, with at last paralysis of the heart itself. In warm-blooded animals the oil produced symptoms precisely similar to those which it causes in man. After section of the spinal cord the convulsions did not occur in the hind legs; they are therefore of cerebral origin. The arterial pressure was not affected until death was at hand: so that it is evident that the drug has little action upon the heart.

**OIL OF HEDEOMA.**—Under the name of *oil of pennyroyal*, in the United States, the oil of the *Hedeoma pulegioides* (*Oleum Hedeomæ*, U. S.) is used as a stimulating emmenagogue in domestic practice, but has very little power. Two fluidrachms taken by a young woman produced vertigo, faintness, muscular weakness, frequent feeble pulse, cold skin, and cold extremities (C. A. Bryce). Dose, from two to ten minims (0.12–0.6 C.c.). In Europe the oil of *Mentha pulegium* is known as *oil of pennyroyal*.

**APIOL.**—Apiol is a peculiar non-nitrogenous, yellowish, oily liquid, which is obtained from the root of the *Apium petroselinum*, or common parsley. According to its discoverers, Joret and Homolle, one gramme of it will produce in man a cerebral excitation very similar to that induced by coffee, without other symptoms. In doses of from two to four grammes it causes a species of intoxication, with vertigo, ringing in the ears, and severe frontal headache,—a group of symptoms very similar to those seen in cinchonization.

Apiol has been used to a considerable extent as an antiperiodic, but it is certainly of very inferior rank. It was originally recommended in *amenorrhœa* by Joret and Homolle, who exhibited three or four grains twice a day for a week preceding the time in which the return of menstruation was due. Whenever any symptoms of the menstrual molimen appear, fifteen grains (1 Gm.) of it should be administered in the course of three or four hours. It is always given in capsules, each of which, as imported from France, usually contains one-quarter of a gramme (3.9 grains).

**POTASSIUM PERMANGANATE**, originally recommended by Sydney Ringer as an emmenagogue, has been very highly commended by

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\* For references to cases see Guillery; also *Cincinnati Lancet Clinic*, 1881; *A. J. M. S.* xvi., xxiii., xxiv.; *Med. Bull.*, 1888, x. Guillery believes that the symptoms caused by the oil and by tansy tea are different. In a case of poisoning by the leaves, however, reported in the *Nashville Med. and Surg. Journ.*, 1879, xxiii., the symptoms were those alleged to be characteristic of oil-poisoning; and the oil probably is the only active principle of the drug.



Fordyce Barker and other physicians.\* Therapeutic doses of the permanganate must be entirely decomposed in a very short time after they reach the stomach, so that any action which the drug exerts upon the general system is due to the manganese oxide; indeed, the ordinary *black manganese oxide* has been affirmed by various practitioners to be as active an emmenagogue as is the permanganate. We have employed these agents to a limited extent in functional *amenorrhœa*, sometimes with, sometimes without, success. The only difference which we have been able to perceive in their action is that the permanganate is the more irritant to the stomach. The dose of either preparation may be set down as one to two grains (0.06–0.13 Gm.),—always administered after meals, in order to avoid, as far as possible, gastric irritation. Cases of severe gastritis produced by the permanganate have been reported.

VIBURNUM OPULUS. U. S.—*Cramp-root*. VIBURNUM PRUNIFOLIUM. U. S. *Black Haw*.—These remedies are believed by various practitioners to be of value in the treatment of *dysmenorrhœa* and *menorrhagia*, and *ovarian irritation*.

Fluidextractum Viburni Opuli..... 1 to 4 fluidrachms (4–15 C.c.).  
Fluidextractum Viburni Prunifolii..... 1 to 4 fluidrachms (4–15 C.c.).

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\* See *Therap. Gaz.*, ii. and iii.

## FAMILY VIII.—OXYTICICS.

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OXYTICICS are those remedies which are employed during or directly after parturition, to increase the uterine action. Of the few drugs which have claims for position in the present class, quinine has already been fully considered; it apparently differs entirely from the other known oxytocics in not producing continuous tetanic spasms of the uterus, and is therefore the safest stimulant to parturition at our command. The peculiar dangers which beset the use in labor of drugs which cause uterine tetanus will be fully discussed in the article upon ergot.

### ERGOT.

Ergot is a blackish body, one to two inches in length, irregularly cylindrical, grooved along one side, and very generally curved; it is composed of very thick walled microscopic cells, containing oil-drops but no starch. As was first demonstrated by Tulasne, ergot is the sclerotium of the *Claviceps* (*C. purpurea*, Tulasne) which infests the grain of *Secale cereale*, or rye.

Among the lowest of vegetable organisms, and distinguished from all other plants by the absence of chlorophyll, are the fungi. There are in most cases two distinct states or stages in the life of a fungus: in the first of these, the vegetating period, it exists as a *mycelium*, a usually filamentous mass or flocculus, whose sole function is to grow and increase; in the second stage the *thallus*, or ordinary fungus or mushroom, is formed, and to it is assigned the function of developing reproductive bodies, after whose maturation it perishes. Between these stages there is in some fungi an intermediate one, in which the plant exists as a *sclerotium*. The genus *Claviceps* comprises a number of parasitic fungi, which develop in the pistils of the various species of Gramineæ. The first appearance of the ergot is in the flower of the rye, at the base of whose pistil there arises a minute flocculent mass of mycelial filaments. These filaments, continually growing and invading all parts of the tissue of the pistil, at last form of it an irregular whitish body, at the base of which after a time appears a dark-colored body, the sclerotium, which continues to grow, lifting up the diseased and withering mass formed out of the original pistil, and finally developing into a perfect ergot. If a fresh, living ergot be placed in a damp, warm place, after a time little cracks will appear in its surface, and through these cracks little round bodies will project, and finally be raised up on stalks and constitute perfect thalli,—minute fungi, which finally produce spores.

Ergot is an exceedingly complex substance, containing nearly thirty-five per cent. of an inert fixed oil.

A large number of chemists have claimed to have isolated the active principle of ergot, only to have their claims denied and replaced by the discoveries of the next chemist who invades the field. Kobert isolated a tetanizing alkaloid to which he gives the name of cornutin, which he found also to be a powerful stimulant to the uterus. He also described an active acid body to which he gave the name sphacelenic acid. Jacobi found a resinous acid sphacelo-toxin which was apparently

identical with Kobert's sphacelenic acid, which forms a number of combinations with other constituents of ergot. Vohlen describes a crystalline body, clavin, which, he claims, stimulates the uterus but does not affect the blood-vessels. Barker and Dale have found a substance, ergotoxin, which they regard as a hydrate of the alkaloid ergotin discovered by Tanret, which they regard as the active principle. To which, if any of these substances, ergot owes its activity it is impossible to say.

The term ergotin has been applied to a variety of substance, but to-day is most commonly understood to refer to Bonjean's ergotin, which is practically a watery extract of the drug.

**Official Preparations :**

Fluidextractum Ergotæ.....	1 to 4 fluidrachms (4-15 C.c.).
Extractum Ergotæ.....	5 to 8 grains (0.3-0.5 Gm.).
Vinum Ergotæ (20 per cent.).....	$\frac{1}{2}$ to 2 fluidounces (15-60 C.c.).

**Physiological Action.**—*Local Action.*—*Absorption and Elimination.*—The preparations of ergot have a very feeble local action, but their irritant properties are sufficient to interfere with their hypodermic use, and sometimes to make them disturb the stomach. They yield their active principles readily to absorption, but concerning the fate of these bodies in the organism we have no knowledge.

*General Effects.*—According to Diez (quoted by Stillé), the principal effects of poisonous doses of ergot are in the lower animals profuse salivation, vomiting, dilatation of the pupils, hurried breathing, frequent pulse, cries, trembling, staggering, paraplegia, in some cases diarrhœa and urgent thirst, convulsions, and death.\*

Among the lower animals chickens are most susceptible to the action of ergot. In these it produces, besides ataxia and general weakness, a cyanosis of the comb and wattle which become, if the dose has been sufficient, finally gangrenous and fall off. So marked is this effect that it has been used as a method of determining the comparative activity of different specimens of the drug. It is asserted that in pigs the tips of the ears become gangrenous. The mortification is due to obstruction of the arteries by a transparent hyaline mass following a local vascular spasm.

The toxic effects of ergot on the lower animals are mainly paralytic, and the only ones which are in any sense characteristic are the anesthesia and the coldness of the surface. As this coldness of the surface has been noted in various women in whom the drug has caused fatal abortion, it is probably characteristic of the poisoning.

*Nervous System.*—The action of ergot upon the general nervous system is extremely feeble, but is not well understood; as both Wright and Köhler have found that the voluntary muscles are not affected by the drug, the motor symptoms of the poisoning would appear to be of nervous origin.\* The statement of Eugene Haudelin, that the peripheral nerves are not affected, has been confirmed by the experiments of Köhler, so far as concerns the motor nerves and the watery extract of the drug.

According to Kobert cornutine acts as a convulsant but sphacelotoxin is a motor depressant. A specimen containing excessive amounts of cornutine may

\* In 1884 T. Korkorin, in a St. Petersburg thesis, affirmed that pronounced and characteristic pathological alterations can be found in the spinal cord of animals slowly killed with ergot. The correctness of this, however, seems to be more than doubtful. See paper by A. Grünfeld (*Archiv f. Psych. u. Nerven.*, 1889-90, xxi).



therefore cause spasms but ordinarily from preparations of ergot itself, as shown by S. A. Wright the paralysis is much more marked than the spasms; in some cases the special senses seemed to be destroyed, and coldness of the surface was a very prominent symptom. He found that the intravenous injection of a strong infusion caused immediate dilatation of the pupils, great increase in the rate of the cardiac pulsations, paralysis, and convulsions and death in a few minutes: when the dose was not sufficient to kill at once, great anesthesia and coldness of the skin and also paralysis of the special senses were developed. In Kersch's experiments intravenous injections of the poison caused marked coldness of the surface and also great muscular rigidity. Upon rabbits, according to Wright, ergot acts very feebly. Enormous doses of ergot are required to produce toxic symptoms in animals, since in one of Wright's experiments an amount equivalent to two drachms for every pound weight of the dog failed to kill.

*Circulation.*—The characteristic action of ergot upon the circulation is to cause a rise of blood-pressure by constriction of the blood-vessels probably through stimulation of the vaso-motor centres. After very large doses the blood-pressure is lowered probably chiefly by weakening of the heart muscle although there may be also a toxic widening of the vessels.

In 1870 Charles L. Holmes found that ergot injected into the jugular vein of a dog caused a sudden immediate fall of the blood-pressure, followed in a short time by a marked rise above the normal. This fact has been confirmed by Köhler and Eberty, by H. C. Wood, by Kobert and by Jacobi. Plumier, however, asserts that the rise is insignificant, and in the experiments of Sollman and Brown it was either absent entirely or else very slight. The most probable explanation of the results obtained in the last two investigations is found in the ease with which ergot undergoes spontaneous decomposition. Houghton examined some two hundred specimens of ergot, many of which he found to be quite inert.

The primary fall of pressure is probably due to the depressant action of an excessive amount of the drug, which reaches the heart in concentrated form when thrown into the vein, directly upon the cardiac muscle.

The rise in pressure, which is to be regarded as the characteristic effect of ergot upon the circulation, is due to a constriction of the blood-vessels. Holmes, Wernich, Vogt, Kersch, Schuller and Boldt assert that they have seen invariably diminution in the caliber of the arteries under the influence of ergot.\* According to Wood, Hemmeter and Kobert the rise in pressure does not occur after section of the spinal cord, and is therefore consequent upon a stimulation of the vaso-motor centre in the medulla.

There is however some evidence that it also exerts some direct stimulant influence on the vessel-walls. The evidence which has been brought forward in favor of the direct stimulant action of ergot upon the blood-vessels fibres consists of the statements of Holmes, Wernich, and J. H. Peton, that after the nerves going to certain blood-vessels have been cut, these vessels can be seen to contract when ergot is injected into the animal. The observations of Holmes, Wernich, and Peton are, however, in distinct contradiction to the very elaborate experiments of Paul Vogt, in which the dilated vessels in the ear of the rabbit whose cervical ganglion had been extirpated could not be made to contract by ergot. Moreover, any observations made with the eye as to the contractions or dilatations of the blood-vessels are of doubtful value.

Greater importance should be attached to the experiments of Ringer and Sainsbury, made upon tortoisés according to the method of Gaskell (see *DIGITALIS*, page 224). In these the addition of ergotin greatly slowed the rate of flow through the arterioles, but in these experiments it was found that the addition of ergotin to

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\* Patrick Nicol and J. Mossop (*Brit. and For. Medico-Chir. Rev.*, 1872, 1) have noted with the ophthalmoscope the contraction of the retinal vessels after the exhibition of ergot in man.

the saline solution used had no distinct effect until there was *ten per cent.* of the extract in solution, enough to seriously influence the viscosity of the solution, and probably the effect of the ergotin was the result of altered physical conditions.

They have, however, received some confirmation in the investigations of Plumier who found that perfusion through the pulmonary vessels separated from the central nervous system produced a slight constriction of these vessels, and of Jacobi, who found that the rate of flow through the vessels of the leg was diminished when perfused with chrysotoxin.

According to the observations of Parola, Gibbon, Beatty (quoted by Stillé), and Bailly and Sée, very large doses of ergot reduce the pulse-rate in man, but only under the rarest circumstances below sixty. Meltzer and Auer observed that under the influence of ergot the vagus is abnormally sensitive to electrical stimulation. Eberty found that in the frog the drug still lessened the rate of the cardiac beats after destruction of the medulla, but that in the atropinized mammal ergot was powerless to alter the cardiac rhythm. By toxic doses the rapidity of the heart's action is increased, and, according to Boreischa, galvanization of the par vagum has at this time little or no effect upon the pulse. It may be that ergot first stimulates and then paralyzes the peripheral pneumogastric, but before any conclusion can be considered established further investigation is imperative.

As has been shown by Haudelin, Boreischa, Brown-Séguard, and others, the toxic dose of ergot produces immediately or after a time a fall of the arterial pressure. The assertion of Brown-Séguard, that this fall of arterial pressure is due, at least in part, to a vaso-motor paralysis, is corroborated by the experiments of Boreischa, who found that when the vessels were paralyzed by section of the spinal cord high up, the fall of pressure produced by the toxic dose of ergot was proportionately not nearly so great as in a normal animal. The fall of pressure however is brought about also through cardiac failure for Hemmeter and Plumier demonstrated that the isolated heart is slowed and weakened by large doses of ergot and Eberty found that the heart is arrested in diastole and non-irritable.

*Bodily Temperature.*—The coldness of the surface in ergotic poisoning seems to depend upon a general fall of temperature. Hemmeter has noticed that this fall of temperature commonly amounts to, and often exceeds, 5° C. in the lower animals and 2° F. in the human being. The cause of it has not been made out. Hemmeter states that in several experiments he has found pronounced reduction of urea elimination in dogs under the influence of ergot, and believes it possible, though not proved, that the fall of temperature is due to diminished general metabolism; it may, however, be only a secondary phenomenon due to the action of the drug upon the circulation.

*Action on the Intestines.*—The muscle-fibres in the coats of the blood-vessels are certainly not the only non-striated muscles influenced by ergot. According to Wertheimer and Magnin, ergot produces active movements in the coats of the stomach, and Wright found very active intestinal peristalsis at the post-mortem examinations of poisoned animals; further, Wernich, Haudelin, and Meltzer and Auer bear witness to the violent intestinal peristalsis produced in the lower animals by toxic doses of ergot.

*Uterus.*—Upon the uterus of parturient women or of the parturient lower mammal ergot exerts a very pronounced and fixed influence, increasing the length and force of the pains, and, if it be given in sufficient dose, causing after a time violent tetanic cramp of the whole organ.

The action of ergot in producing contraction in the impregnated but not parturient womb is by no means so constant. Clinical experience shows that in pregnant women it often fails to originate uterine contractions. Upon animals Wright found it to fail in all of a number of trials, as did also Bonjean in a single experiment. On the other hand, Diez,\* Oslere,\* and Percy and Laurent\* found it to cause abortion in guinea-pigs, sows, rabbits, cows, and cats; and Bodin has reported an epidemic of abortion occurring among cows near Trois Croix, which he attributed to feeding upon ergotized grasses.

Our present knowledge indicates very strongly that the uterine contractions produced by ergot are of centric origin. It is true that some years ago Boreischa asserted that he had succeeded in producing violent uterine movements with ergot after division of the nerve connections of the organ, but the result reached by Wernich—namely, that no vermicular movements are produced in the unimpregnated womb after previous section of the spinal cord—has received confirmation from John C. Hemmeter. In repeated experiments, having found that the injection of ergotin produced contractions in the exposed uterus of a narcotized rabbit, he destroyed the spinal cord with a hot wire, and determined that ergot was no longer able to cause uterine contractions: that the failure of the ergot in these cases was not due to paralysis of the uterus by shock was then demonstrated by injecting ammonia into the veins, when violent uterine contractions occurred.

**SUMMARY.**—Therapeutic doses of ergot increase blood-pressure by stimulating the vaso-motor centre in the medulla, but have no distinct influence upon the heart or the walls of the arterioles. Toxic doses depress the pressure by cardiac paralysis, and probably also by paralysis of the blood-vessels. Ergot, in full therapeutic doses, so acts upon the centres in the lower spinal cord which preside over the uterine muscles as to produce in the parturient womb violent uterine contractions, and finally uterine tetanus. It also increases the peristaltic movements of the stomach and intestines.

**Therapeutics.**—Ergot has been used in medicine chiefly for three purposes: (1) to increase the uterine contractions, (2) to check hemorrhage, (3) to contract the blood-vessels in chronic congestions and over-secretions depending on vascular relaxations.

1.—Owing to the power that ergot possesses of intensifying labor-pains, it has long been used in *uterine inertia* during parturition. Indeed, it was for this purpose that the drug was first employed in medicine, and thereby acquired the name of *pulvis parturiens*. The literature of the subject is immense, and all imaginable opinions as to the effects of the drug when given in labor, and as to the advisability of its employment, have been advanced; but, without discussing these, we shall here simply point out the clearly established

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\* Quoted by Stillé (*Therapeutics*, 2d ed., ii. 585).



rules for its use and the clinically determined dangers and advantages of its employment. If ergot be given in very small doses during labor, the natural pains are simply intensified; but if the dose be large enough to have a decided effect, their character is altered: they become not only more severe but much more prolonged than normal, and finally the intervals of relaxation appear to be completely abolished and the intermittent expulsive efforts are changed into one violent, continuous strain. It is evident that, if the resistance be sufficiently great, this may endanger the safety both of the mother and of the child. The dangers to the mother are twofold: there is a possibility of the uterus rupturing itself by its efforts; and, when the head comes down upon the perineum, if the soft parts be rigid there is a very strong probability that they will be lacerated. The danger of uterine rupture is, we think, a remote one; for although several alleged cases have been recorded, yet in very few is the accident clearly traceable to the asserted cause. The fatal character of the accident is such, however, that the possibility of its occurrence should always prevent the reckless use of the drug.

The improper use of ergot is even more serious in its effects upon the child than upon the mother. During a violent uterine contraction the passage of the blood from the placenta to the child must be interfered with, or, in other words, the respiration of the foetus is temporarily stopped, so that its life depends upon the aëration of the blood during the intervals. If the latter be very much shortened, the life of the child is greatly imperilled; and if they be abolished, it must be destroyed, unless delivery occurs in a very few moments. These considerations are, we think, sufficient, without further discussion, to show the imperativeness of the rule *never* to give ergot in uterine inertia when there is much *resistance*, either in the bony or in the soft parts of the mother. In primiparæ such resistance is always to be looked for, and its degree often difficult to judge of beforehand; and in such women ergot should not be used for the purposes of expulsion. Even under the most favorable circumstances—when the woman has previously borne children, when the bony pelvis is capacious, and the soft parts are relaxed and dilatable—its use should be entered upon with caution; and if the accoucheur be skilful in the application of instruments, cases must be rare in which the latter are not preferable to the ecbotic.

In women of lax fibre, with roomy pelves, ergot may be cautiously used in uterine inertia if instruments are not at hand, or if they are objected to, or if the obstetrician is timid in their application.

At the close of parturition, ergot is very commonly employed to prevent *post-partum hemorrhage*; and in this case there is no objection to its use, and the remedy is invaluable. But, as it requires from fifteen to twenty minutes for its action when given by the mouth, ergot exhibited in this way cannot be relied upon to arrest flooding when it has already set in. To prevent the occurrence of the latter, it is an excellent rule to give a full dose of the ecbotic when the child's

head is well down upon the perineum and beginning to emerge at the vulva. After labor, if a tendency to bleeding is manifested, ergot may be administered hypodermically.

For the induction of *premature labor*, ergot has been and still is to some extent used; but it is uncertain in its action, and offers no advantages over instrumental methods.

In 1872 Hildebrandt announced that in nine cases of *fibroid tumors* of the uterus he had used with the utmost advantage hypodermic injections of ergotin, and this practice has been followed very widely on this continent. It is scarcely to be doubted that cures are sometimes effected; but probably in the majority of cases\* the drug simply lessens the uterine congestion, and does good precisely as it does in *chronic* or *subacute metritis* and in *subinvolution* and *hypertrophy* of the uterus (Meadows); it may be that sometimes it strangles the growth by causing uterine contractions. If the latter be the case, a cure, as is suggested by Goodell, is to be expected from the remedy only in mural and sub-mucoid tumors.

2.—The success of ergot in arresting hemorrhage after labor soon led to its use in uterine hemorrhages in other than parturient or pregnant women; and the next step beyond this was its employment in other hemorrhages. In all forms of *hemorrhage* in which no direct local application can be made, ergot is to-day still largely used. The use of ergot as a styptic in an internal hemorrhage is based on its power of contracting blood-vessels. It must be remembered however that any substance which leads to a general vaso-constriction increases the force of the circulation. The increased pressure tends to dislodge any clot which may be formed at the bleeding point. Therefore those drugs which narrow the lumen of the vessels must incline to continue rather than check internal hemorrhages. In uterine hemorrhages it acts by causing contraction of the uterus itself, not of the blood-vessels.

3.—Very many years ago F. E. Barlan-Fontayral proposed the use of ergot in *chronic dysentery* and *diarrhœa*, on account of its power of causing contraction of the capillaries; and Massolaz, in an epidemic of chronic diarrhœa among the French troops serving in the East, found that the suggestion was well timed. Although Barlan-Fontayral afterwards published a book upon the subject, it attracted little or no attention. In 1871 A. Luton, of Rheims, stated, as something new, that he had used ergot with remarkable success in a violent and protracted epidemic of *dysentery*. Successful cases of *chronic diarrhœa* are also reported by other observers, so that trials of the remedy should be made in all obstinate cases.

In colliquative *night-sweats* due to relaxation of the blood-vessels, ergot is a most efficient remedy. Another employment of ergot for the purpose of restraining excessive secretion is in *galactorrhœa*, in

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\* See *Amer. Journ. Med. Sci.*, July, 1873; *Amer. Practitioner*, May, 1873, May, 1874, August, 1874; *Clinic*, April, 1873; *Lancet*, May, 1873; *Chicago Med. Journ.*, 1874; and especially Byford's Address (*Trans. Amer. Med. Assoc.*, 1875).

which affection it has been used with success by Le Gendre, who was led to employ it by an observation of Poyet and Commarmond, that wet-nurses fed upon ergotized bread lost their milk.

The action of ergot upon the blood-vessels suggests its employment in those cases in which there is local or general dilatation of the vessels. We have used it in pulmonic congestion with apparent good results, and it has been highly lauded in the first stages of *pneumonia* by N. S. Davis, by Sunol, and later by other clinicians. It has been especially noted by J. E. Kelly, as giving immediate relief when injected hypodermically in low forms of *pulmonary hyperemia*, such as occur in typhoid fevers. Ergot has also been recommended by O. Rosenbach, as a means of raising blood-pressure in cases of cardiac disease where there is thought to be insufficient peripheral resistance; and Hemmeter believes that the dicrotic pulse is due to a very low degree of pressure in the arterial system, and is an indication, especially in chronic cardiac disease, for the use of ergot. Rosenbach recommends the drug strongly in aortic insufficiency with cardiac dilatation. Ergot would seem to be indicated as a vaso-motor stimulant in *surgical shock*, but is much less prompt in its influence than atropine.

As originally suggested by Brown-Séquard, it is still much used for the relief of chronic *cerebral and spinal congestion*. When there is a rupture of the vessels, as in *apoplexy*, by increasing the blood-pressure it tends to do harm rather than good. It is largely used for the relief of *congestive headaches*, and has been employed in *epilepsy*, in which disease, according to Hemmeter, it greatly increases the efficiency of the bromides. Dehenne states that he has obtained most remarkable effects in the relief of *diabetes* by subcutaneous injections of ergotin. The general clinical experience, however, seems to be that while occasionally ergot does great good in diabetes, it usually fails to accomplish anything. When successful, it rapidly diminishes the glycosuria, thirst, and polyuria. In *diabetes insipidus*, though it often fails, ergot is perhaps the most generally useful remedy that we have.

Da Costa has used ergot with asserted good results in *enlargement of the spleen* from various causes and affirms that he has even cured *leukemia* with it.

**Toxicology.**—Even the largest therapeutic doses (an ounce of the fluidextract) produce in man no perceptible symptom save some nausea. In a number of cases death has resulted from abortion caused by large doses of ergot, but we know of but two instances of serious poisoning in a non-pregnant person.\*

In the first case gastric irritation, thirst, diarrhœa, burning pain in the feet, and convulsions are said to have preceded death. In the second case (G. S. Oldright), two hours after taking the drug (amount not stated) there were developed tingling in the fingers and feet,

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\* Davidson reports a case with fluid blood, jaundice, and universal hemorrhages, attributed with doubtful correctness to poisoning by ergot (*London Lancet*, 1882, ii. 526).



cramps in the legs, arms, and chest, with dizziness and weakness; the pupils were dilated, the pulse was very small, and a feeling of coldness was complained of. These symptoms were relieved by the administration of stimulants and the use of external heat; after a time they recurred with greater violence; finally, under the reinstitution of the measures previously employed, the face became intensely congested and purplish red, pain in the head was felt, the patient seemed much excited, and convulsions were feared, but did not occur; there was some diarrhoea, with dark gray stools.

*Chronic Poisoning.*—Since the days of Galen there have swept over larger or smaller districts of Europe epidemics of diseases which have been attributed to ergot. In many parts of Europe rye bread forms the great staple article of food of the lower classes. It always contains a small quantity of ergot, but not enough to have any deleterious effect upon the health. When the summer is wet and cold, the rye becomes very extensively ergotized, so that the fungus constitutes a large proportion of the materials entering into the bread. It is under these circumstances that there occur epidemics of *ergotism* or chronic ergotic poisoning. It is not always the rye that causes these frightful losses of life, as Heusinger has traced one epidemic to diseased oats. Before going further, it seems proper to state that Trousseau and Pidoux assert that these epidemics are not dependent upon any specific action of ergot, but are either epidemics of blood diseases or simply the results of improper and insufficient food,—the outcomes of poverty, wretchedness, and famine. It seems to us indisputable that some of the various epidemics which have been recorded were of this character, but certainly it is no less indisputable that others were not. Moreover, numerous scattered cases are on record in which a few persons or a family have been affected with ergotism unmistakably traceable to the use of bread largely composed of the fungus.\*

The scope of the present treatise is such as to forbid our entering into an elaborate discussion of the epidemics of ergotism, especially as the subject has no practical bearing so far as the American profession is concerned, since the absence of deep poverty is so complete in our country that no one would feed on largely ergotized bread; and, in fact, no case of ergotism has as yet been recorded as occurring in the United States.†

There are two varieties of ergotism,—the gangrenous and the spasmodic. In some epidemics the cases have been of mixed type.

*Gangrenous ergotism* has been especially observed in France, and is believed to be the same as the *Ignis Sacer* or the *Ignis Sancti Antonii* of the Middle Ages,—an affection which in 922 killed forty thousand persons in Southwestern France, and in 1128–29 fourteen thousand in Paris alone. It generally commences with itching and formications in the feet, severe pain in the back, contractions in the

\* For an account of a modern epidemic, see *Deutsch. Arch. f. Klin. Med.*, xxxiii. 246.

† Any one especially interested in the subject will find the literature very well represented in the references of Stillé's work on Therapeutics, Duboué's *Recherches sur les Propriétés Thérapeutiques du Seigle Ergoté*, Paris, 1873, and Husemann's *Handbuch der Toxicologie*.

muscles, nausea, giddiness, apathy, with abortion in pregnant women, in suckling women drying of the milk, and in maidens amenorrhœa. After some time deep, heavy, aching pains in the limbs, an intense feeling of coldness, with real coldness of the surface, profound apathy, and a sense of utter weariness develop themselves. Then a dark red spot appears on the nose or on one of the extremities; all sensation is lost in the affected part; the skin, perhaps over a large surface, assumes a livid red hue, and in the foci of local changes bullæ filled with serum appear. The adynamic symptoms, in severe cases, deepen as the gangrene spreads, until finally death puts an end to the scene. Very generally the appetite and digestion are preserved to the last, and not rarely there is an almost ferocious hunger. The gangrene is generally dry, the parts withering and mummifying; but sometimes it is moist, and pyemic symptoms may even be developed. Of course a very large number of cases do not terminate in death; but the part immediately affected is generally lost. In these cases the toes most generally are the portion destroyed, but it may be any one or all of the extremities; and the nose, lips, ears, and even the buttocks sometimes bear the brunt of the disorder.

*Spasmodic ergotism* may in the lightest cases be manifested only by itching, formications, numbness, or complete anesthesia of the fingers and toes or of the buttocks, and by gastro-intestinal irritation, as shown by colic, vomiting, diarrhœa, or constipation, and withal a ravenous hunger. In more severe cases these manifestations are intensified, and spasmodic symptoms appear, violent and painful tonic contractions affecting especially the flexors of the extremities, interrupted at times by intervals of quiet, but gradually growing into severe general tetanic paroxysms, with opisthotonos and emprosthotonos. In the intervals there are very generally muscular tremblings, and as the case progresses there are developed cerebral manifestations, such as disturbances of vision, photophobia, chromopsia, hemiopia, and periodic amblyopia and amaurosis, giddiness, cataleptic and epileptic paroxysms with or without loss of consciousness, delirium, and idiocy. Gastro-intestinal symptoms are always very marked, but with them are a characteristic ravenous hunger and a longing for sour food and drink. The skin is earthy or yellowish in tint, and is often spotted with boils or pustules or semi-gangrenous vesicles. Death is apparently caused by exhaustion; and in those that recover, various local paralyses, habitual spasms, amaurosis, mental aberrations, or even idiocy often remain through life. In a few cases the symptoms are still more violent, and the spinal and cerebral disturbances soon lead to death.

The primary changes in ergotism are in the blood-vessels. Ergotic gangrene can readily be produced in the comb and tongue of chickens, and Von Recklinghausen asserts that the essential lesion in these cases is hyaline thrombi in the arterioles and capillaries; while Grünfeld has found the walls of the vessels thickened, structurally changed, and their lumen occupied by thrombi which in some places are full of blood-corpuscles and in other parts undergoing hyaline degeneration.

**Administration.**—If used in nervous diseases ergot should be given in large dose; thus in congestion of the spinal cord we usually begin with half an ounce (15 C.c.) of the fluidextract and increase it to an ounce three times a day.\* Extract of ergot is preferable to the fluidextract when time is not important, as being less likely to cause nausea. When administered by the mouth, it should be given in capsules; when used hypodermically, five grains should be dis-

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\* It would appear that sometimes, owing to idiosyncrasies, even small amounts of ergot cause much disturbance. Thus, R. B. Faulkner reports (*New York Med. Journ.*, June 14, 1884) a case in which a fluidrachm of the fluidextract caused great sleepiness, swelling and redness of the feet, and violent pricking of the extremities, probably as the outcome of gastric irritation.

solved in five minims of glycerin, fifteen minims of boiled water, and one-fourth of a minim of phenol, and filtered: the danger of causing severe local trouble is lessened by plunging the nozzle of the syringe deeply into the muscular tissues.

The attempt to assay preparations of ergot by their action upon the comb of the cock is of doubtful utility; it is at present uncertain whether the action of ergot upon the uterus and upon blood-vessels is due to one or to several more or less antagonistic substances.

### HYDRASTIS.

The rhizome and roots of *Hydrastis Canadensis*, an indigenous perennial, commonly known as *Golden Seal*. *Hydrastis* contains the alkaloid *berberine*, to which it owes its yellow color, and probably also two other alkaloids, *canadine* \* and *xanthopuccine*, besides its characteristic alkaloid, *hydrastine*.† The latter occurs in brilliant four-sided prisms, inodorous and almost tasteless, but having a very bitter and somewhat acrid taste when in the form of a salt. Pure hydrastine and its salts can be obtained in the shops, but the *hydrastin* of commerce is an impure body containing berberine, hydrastine, and probably other more or less active alkaloids besides resin.

#### Official Preparations:

Fluidextractum Hydrastis.....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Glyceritum Hydrastis.....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).
Tinctura Hydrastis (20 per cent.).....	1 to 2 fluidrachms (4-8 C.c.).
Hydrastina.....	$\frac{1}{8}$ to $\frac{1}{2}$ grain (0.01-0.03 Gm.).

**Physiological Action.**—There appear to be no cases on record of serious poisoning from any of the alkaloids of hydrastis, and in the only case of poisoning by the crude drug, nine grammes of the fluidextract produced vomiting, giddiness, headache, dyspnœa; a slow, weak, irregular pulse, mydriasis, and hallucinations of sight (Friedeberg). The alkaloid hydrastine is so dominant in its action, that to it is chiefly due the influence of the crude drug.

*Berberine* is an inactive alkaloid, Buchner having taken twenty grains with very little effect. In doses of from two to five grains (0.1-0.3 Gm.) it is a simple bitter, and as such may be given in pill or alcohol.

Toxic doses of berberine cause in the lower animals diarrhœa, rapid loss of flesh, tremors, diminished respiratory action, progressive paralysis, lessening of the pulse-rate, depression of the arterial pressure, partial anesthesia, albuminous or bloody urine, and in some cases final convulsions. (Falck and Guenste; Mosse and Tautz.) After death hemorrhagic nephritis may be found. Both Schurinow and Curci agree that berberine causes the arterial pressure to fall rapidly from vaso-motor paralysis; the peripheral vagus is paralyzed. (Schurinow, Marfori,

\* According to the experiments of Bunge, *canadine*, in toxic doses, produces a brief stage of psychical and motor excitability, followed by general paralysis and depression, with death from respiratory paralysis, and has little direct action upon the blood-pressure. The rate of pulsation in the isolated frog's heart is lessened, but the work done is not decreased by the moderate dose; larger doses paralyze the muscle of the heart. The voluntary muscles are not affected by the alkaloid, nor is the uterus, although diarrhœa with violent intestinal peristalsis is produced.

† For an article on the chemical and physiological activities of a number of derivatives from hydrastine by Falck, see *Virchow's Archiv*, 1895, cxlii.



denied by Curci.) According to Curci, the heart-muscle is directly affected. Schurinow and Mosse and Tautz are in accord in asserting that the nerve-trunks are especially implicated in the poisoning, but Curci believes that the motor and sensory disorders are due to an action upon the spinal cord; probably both the cord and the nerve-trunks are affected.

*Hydrastine* causes, in animals, increased, followed after a time by lessened, respiratory movements, salivation, vomiting, excessive peristalsis, muscular tremblings, weakness and rigidity, loss of voluntary movement, rise of bodily temperature (Bunge) (often followed by a fall), feeble, rapid pulse, clonic and tetanic convulsions, increased reflex activity, and death from cramp-asphyxia or general paralysis, or exhaustion with respiratory failure. Hydrastine is probably eliminated through the kidneys. (See Phillips and Pembrey.)

In a research upon the effect on the lower animals of the long-continued use of hydrastine and *hydrastinine*, J. De Vos found that these alkaloids have no cumulative action, but that gradually the animals seem to become accustomed to their use. Neither of them in any way disturbed the gastric or intestinal digestion. Albuminuria never occurred, nor was there apparent disturbance of assimilation.

*Nervous System.*—So far as is known, hydrastine has little or no action upon the cerebral hemispheres, but is a powerful stimulant to the motor side of the spinal cord. Death may occur during the period of violent convulsions with heightened reflex activity; but if the animal survives, there follows a general paralysis, which, as the alkaloid is a marked depressant to the motor nerve-trunks, is probably of peripheral origin.

According to Cerna, when voluntary movements and the reflexes are first depressed in the frog, the reflexes can be restored by section of the cord, so that the palsy is probably due to stimulation of Setschenow's centre; later it is irremediable. Late in a protracted poisoning, and after death, the motor nerves are depressed or altogether paralyzed (Falck, Cerna), and Bunge has found that the local application of a solution of the alkaloid to a nerve kills it. According to Falck, hydrastine placed in the eye has no effect upon the sensitiveness of the conjunctiva, but both Slavatinski (quoted by Bunge) and Mays affirm that late in the poisoning there is general loss of sensibility. Mays further states that when brought in contact with a nerve-trunk, hydrastine paralyzes its sensory fibres, although tying an artery does not prevent the development of anesthesia in general poisoning by the alkaloid. If these experiments be correct, the alkaloid acts both upon the sensory cord and sensory nerve; this action, however, is entirely subordinate to its influence upon the motor tract.

*Muscles.*—Upon the muscles the alkaloid has some influence, since both Falck and Bunge have found that its not too dilute solution directly applied to a muscle destroys its contractile power, a conclusion which is confirmed by Cerna, who further states that preceding the depression there is a stage of excitation in which the muscular contraction under stimuli is more complete and prolonged than normal.

*Respiration.*—When death takes place during a convulsion, it probably is due to cramp-asphyxia; but when it occurs during the

paralytic stage, it is from paralytic-asphyxia (probably, in part at least, of centric origin), the heart-beat continuing after death (Serdzeff).

*Circulation.*—The characteristic primary effect of a full dose of hydrastine upon the circulation is a rise of the arterial pressure with slowing of the pulse-rate, this condition being followed after a time, if the dose has been toxic, by a fall of the arterial pressure. The rise of the arterial pressure is probably due in part to a direct action upon the heart itself and in part the result of contraction of the blood-vessels, caused probably by an action upon their muscle-fibres. Marfori believes that the vaso-motor centres are also stimulated, but at present this is only a probability. The fall of the arterial pressure is in part of cardiac origin, there being in the later stages of the poisoning a depression of the heart muscle, which ends in diastolic arrest with loss of muscular irritability.

Although W. W. Williams failed to obtain any but the most insignificant rise in blood-pressure from hydrastis the observations of Bartholow, Fellner Falck, Marfori and Pellacani would seem to establish that,—when hydrastine in sufficient dose is injected directly into the circulation there is an immediate fall of pressure, followed by a marked and long-continuing rise unless the original dose has been excessively large, when the pressure falls progressively until death. The primary fall of pressure does not occur after subcutaneous injections (Falck), and is due to direct action of the concentrated drug upon the heart. That the rise of pressure is partly of cardiac origin is proven by the following facts: Marfori, also Phillips and Pembrey, have noted that when hydrastine is applied to the isolated frog's heart it produces slowing of the rate with increased amplitude and power of the cardiac beat, and Serdzeff has proven an actual increase in the work of the isolated heart. Further, the rise of the arterial pressure is not prevented in the mammal by previous section of the splanchnic nerve or of the spinal cord high up (Fellner). Again, Cerna found that the slow pulse of the hydrastine-poisoning occurs after section of the pneumogastric nerve; also, that the vagi nerves retain their power up to the fatal issue; the slow pulse, therefore, is not of inhibitory origin. That the vessels are contracted is indicated by the oncometrical experiments made by Marfori upon the dog's kidney, in which the contraction of that organ was found to be a constant phenomenon of the early stages of hydrastine-poisoning.

It is probable that both voluntary and involuntary muscle-fibres show the primary stimulating influence and the later depressing power of hydrastine, and that the action of the drug upon the circulation is the same as that upon the uterus and the voluntary muscles, only that the voluntary muscle-fibres are less susceptible to its action than are those of involuntary life.

*Abdominal Action.*—It is probable that hydrastine influences both the glands and muscular fibres of the alimentary canal. According to Cerna, it markedly increases the secretion of saliva and of bile, also the intestinal peristalsis.

*Uterus.*—As long ago as 1883 Schatz called attention to the practical value of hydrastis in all forms of hemorrhage from the womb. As the result of experiments upon the lower animals, both Fellner and Slavatinski affirm that hydrastine has a distinct ecboic action, causing uterine contractions in the non-pregnant uterus and abortion in pregnant rabbits. Slavatinski reports a case of premature labor

produced by hypodermic injections of two or three grammes repeated daily. It would seem, therefore, that hydrastine is an ecbolic, and that it arrests uterine hemorrhage in part, if not altogether, by provoking muscular contractions.

*Eyes.*—Hydrastine locally applied to the eye causes at first contraction and afterwards dilatation of the pupil (Cerna).

*Absorption and Elimination.*—Hydrastine appears to be absorbed from the alimentary canal somewhat slowly; at least it is stated by Bunge that ten times as much of it is required to kill an animal when given by the mouth as when injected hypodermically. Marfori states that it is apt to have a cumulative action when given for a length of time. It escapes unchanged through the kidneys, and has also been found by Hirschhausen in the feces.

**SUMMARY.**—Hydrastis is a powerful stimulant to the spinal cord, which in toxic doses is secondarily depressant. The final paralysis is also, at least in part, the outcome of depression of the motor nerves and also of the muscles themselves. The arterial pressure is first elevated and secondarily depressed: the first rise of pressure is probably due to the stimulation of the heart-muscle, increasing the output of force, and of both the vaso-motor centres and the muscle-fibres in the arteriole coats, causing contraction of the blood-vessels: the fall of pressure is the result of a direct paralytic action exerted upon the muscle-fibres in the heart and in the arterioles. Hydrastine notably increases intestinal peristalsis, and probably uterine contractions. It would seem to be a universal muscle-poison, which acts upon both striated and non-striated muscle-fibres in the heart, arterioles, intestines, uterus, and generally throughout the body; its first stimulant action being followed by marked depression.

**Therapeutics.**—When locally applied, the preparations of hydrastis have a very remarkable effect upon the mucous membranes. They have been used with asserted excellent results in *chronic gastrointestinal catarrhs*, especially those due to alcoholic excesses. In the second stages of *gonorrhœa*, after the acute inflammation has been subdued, injections of hydrastin, or the fluidextract, suspended in mucilage, are often of service; ten to twenty minims of the fluidextract may be used to the ounce of fluid. It is also asserted by various specialists that in *otorrhœa*, *nasal*, *vaginal*, and other *mucous catarrhs* the remedy is locally of great value. In *dyspepsia* it has been used as a stomatic stimulant, and has received especial praise in the *vomiting of pregnancy*. At present it is not known to which of the various ingredients of hydrastis these local effects are chiefly due, so that a preparation of hydrastis is preferable to the pure alkaloid.

Hydrastis has been used to a considerable extent, with asserted good results, in various uterine fibroids, menorrhagia and various forms of hemorrhage from the womb. For internal or general medication, as contrasted with the local use of hydrastis, the alkaloid or its



salts is much preferable to the cruder preparation. As anti-hemorrhagic or ecbotic, the alkaloid *hydrastine* may be used in doses of from one-sixth to one-half grain (0.01–0.03 Gm.).

### HYDRASTININE HYDROCHLORIDE.

Hydrastinine is an artificial alkaloid first produced by Martin Freund by the oxidation of hydrastine. The hydrochloride is a light yellow crystalline powder, somewhat deliquescent, odorless, having a bitter saline taste, soluble in 0.3 part water and three parts alcohol.

Hydrastininæ Hydrochloridum. . . . .  $\frac{1}{4}$  to  $1\frac{1}{2}$  grains (0.05–0.1 Gm.).

*Absorption.*—Bunge has found that hydrastinine is readily absorbed and eliminated unchanged, chiefly with the urine, but also to some extent with the saliva, bile, and intestinal secretions. It did not appear to increase the amount of bile secreted.

*Physiological Action.*—In mammals hydrastis causes hyperesthesia, general tremors, rapid pulse, and dyspnoea, followed by paresis, which is said primarily to affect the front legs and to pass into general paralysis with dilated pupils, lowered temperature, and death from failure of respiration. According to Bunge, intestinal peristalsis is markedly increased by hydrastinine.

*Nervous System.*—Hydrastinine is a depressant to the psychomotor area in the brain and also to the motor ganglia in the spinal cord. It also probably lessens the irritability of the peripheral motor nerves and voluntary muscles.

It has been found by W. Kiselew that the excitability of the motor cerebral cortex progressively decreases with progressively increasing doses of hydrastinine, although it never entirely disappears; and that the white substance of the brain is affected similarly to but less powerfully than the gray matter. Kiselew has also confirmed the previous observation of Tarchanoff, that the alkaloid arrests or greatly diminishes the convulsive attacks in epileptic guinea-pigs. It is further worthy of remark that Kiselew, in a few cases of human *epilepsy*, obtained favorable results from the administration of 0.01 to 0.03 gramme of hydrastinine four times a day.

It seems at present doubtful whether there is or is not an early stage of spinal excitement, since Archangelsky affirms that there is increase of susceptibility to touch and to pain in the frog after small doses, while Marfori states that there is no increase of the reflex activity at any time. If there be any stage of excitement, it cannot be well pronounced. It is affirmed that hydrastinine is the natural antagonist of strychnine, and Marfori asserts that the paralysis is of purely central origin. This, however, seems to be incorrect, for not only, as Archangelsky found, is the excitability of the voluntary muscle lessened by the toxic dose of the alkaloid, but Bunge has shown that both the peripheral nerves and the muscle-fibres were paralyzed by a local application of the hydrastinine solution.

In the advanced poisoning the respiratory centre seems to show the depressing influence of the alkaloid, and hence respiratory failure; but here again, according to Archangelsky, especially when the dose has not been too large, there is a period of primary centric stimulation.

*Circulation.*—All observers are in accord in stating that the blood-pressure is increased by the large dose of the alkaloid. The increase appears to be in part of cardiac and in part of vascular origin.

Both Marfori and Bunge, in experiments made with the Williams apparatus, found that the systolic impulse of the isolated frog's heart becomes abnormally strong under the influence of the drug, and that the amount of the heart's work is distinctly increased. W. W. Williams concludes, from rather insufficient experimental data, that the rise of pressure from hydrastinine is chiefly of cardiac origin. But there is evidence that there occurs also a contraction of the vessels, which, according to Marfori, may become so great as entirely to arrest the renal secretion. As the result of elaborate experiments made with section of the splanchnics and of the spinal cord, Archangelsky reaches the conclusion that the contraction of the vessels is chiefly of peripheral origin,\* although there is at the same time some stimulation of the vaso-motor centres in the medulla,—a conclusion concordant with Marfori's results.

When the amount of the hydrastinine has not been too large, the elevated arterial pressure gradually returns to the normal (Bunge); but after a fatal dose of the alkaloid a pronounced fall of pressure finally comes on, apparently as the result of the paralysis of progressive asphyxia, since artificial respiration will bring back the pressure to the normal (Marfori): further, it is asserted by various observers that the heart is finally arrested in systole, so that it would seem that hydrastinine differs from hydrastine in not being a cardiac paralyzant in any dose.

*Pupils.*—Archangelsky has noted that one to two drops of the ten-per-cent. solution of a salt of hydrastinine in the eye will produce a dilatation of the pupil, which reaches its maximum in two to three hours, and remains twelve to fifteen hours.

*Uterus.*—The effect of hydrastinine upon the uterus was studied in pregnant and puerperal dogs, cats, and rats by Archangelsky, who found that it produced rhythmic contractions, independent of any vaso-motor influences, apparently by stimulation of the uterine walls. On the other hand, Bunge, having failed in two experiments to provoke abortion or uterine contractions in pregnant animals by large or even fatal doses of the alkaloid, affirms that it is not an ecbolic. Nevertheless, Faber, as the result of a number of trials, states that hydrastinine given hypodermically during human labor very notably increases the force and length of the uterine contractions, causing a spasm which affects all portions of the uterus, and which is similar in character to that provoked by ergot. In some of the cases there was uterine tetanus, lasting as long as fifteen minutes. Faber also asserts that distinct contractions can be produced in the unimpregnated womb.

*Therapeutics.*—Hydrastinine is used in medicine chiefly for those complaints for which it was originally recommended by Falck,—namely, *menorrhagia*, *metrorrhagia*, congestive *dysmenorrhæa*, and even *endometritis*. The testimony in favor of its arresting uterine hemorrhage in all forms is, on the whole, very consistent, and is abundant, but it is also believed by many gynecologists to have some alterative influence upon the mucous membrane of the uterus. It is affirmed by some gynecologists, but denied by others, that it is an active oxytocic, and exerts its influence upon impregnated and

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\* The assertion of Bunge, that because in heavily chloralized animals hydrastinine fails to elevate the pressure, therefore it acts chiefly upon the vaso-motor centre, is a *non sequitur*, as chloral acts upon the whole circulatory apparatus. Moreover, Bunge's own experiments show that the alkaloid lessens the size of the spleen by contracting the blood-vessels.

unimpregnated wombs largely by causing muscular contractions. It will be seen that the range of its usefulness in gynecology is entirely similar to that of hydrastine; it has, however, acquired popular favor more rapidly and decidedly than the natural alkaloid. It may possibly be more effective as an ecboic, but its superiority probably lies in chief part in its being distinctly less toxic and producing cardiac stimulation rather than cardiac depression. When an immediate impression is desired, the sulphate should be given hypodermically. When a prolonged continuous action is required, it may be administered by the mouth. The results obtained by Kiselew demand a fair trial of it in *epilepsy*. Hydrastinine has some value as a subsidiary cardiac tonic; it does not belong in the same class as digitalis, but its tonic influence is often decidedly helped by its cardiac action.

**GOSSYPH CORTEX.**—The root of the ordinary cotton-plant, the *Gossypium herbaceum* and other cultivated species of *Gossypium*, is said to be used by the negroes in various portions of the South as an *abortifacient*, and Bouchelle, as long ago as 1841, affirmed that it has medical properties similar to those of ergot. It has not, however, come into general use, and our knowledge of its properties is very scanty and uncertain. In the experiments of I. C. Martin enormous doses produced heaviness and stupor in both frogs and mammals, but did not cause abortion in pregnant guinea-pigs or rabbits: On the contrary, Mohr produced abortion in a cat with three doses of 20 C.c. each of the fluidextract. H. I. Garrigues has found cotton-root a serviceable agent in arresting hemorrhage and ameliorating the other symptoms of *uterine* polypoid and fibroid tumors, and even of *uterine cancer*. He insists that the commercial fluidextract is inert and the decoction must be freshly prepared. The oxytocic dose of a decoction (four ounces in a quart of water boiled to a pint) is stated to be a wineglassful, to be repeated every thirty minutes as necessary. The remedy has also been employed in *amenorrhœa* and in *dysmenorrhœa*, in which diseases from three to five grains of a solid aqueous extract have been given three times a day. The fluidextract may be used in doses of a fluidrachm (4 C.c.). *Absorbent Cotton* (*GOSSYPH PURIFICATUM*) is ordinary cotton wool deprived of impurities and fatty matters. It is used mechanically, and as an absorbent.

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## FAMILY IX.—IRRITANTS AND COUNTER-IRRITANTS.

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### IRRITANTS.

IN the treatment of diseases of the skin various irritating substances are used for the purpose of stimulating the nutritive activity of the diseased part. The most important of these drugs are noticed at this place.

SOAP.—Under the name of *Sapo* the U. S. Pharmacopœia recognizes ordinary white *castile soap*, a combination made between olive oil and soda, and consisting chiefly of a mixture of sodium oleate and palmitate. This soap is entirely free from irritant properties, and is used externally as a detergent and sometimes internally in combination with laxatives to render their action milder and perhaps more effective.

SOFT SOAP (*Sapo Mollis*) or *Green soap*, as it was formerly called, is made by the action of potassium hydroxide upon linseed oil; more potash being used than is necessary for the neutralization of the fatty acids, so that the resulting combination is not only strongly detergent but also irritant; and even mildly caustic. Formerly, when vegetable oils contained much chlorophyll, this soap had a distinct greenish color, but as now prepared it is a brownish or yellowish semifluid mass, which yields a nearly clear solution with five times its weight of hot water. It is used chiefly in the treatment of *eczema*. It destroys fatty matter rapidly, softens down exudation, and markedly affects the nutrition of the skin.

CHRYSAROBIN.—Under the name of *Goa Powder*, *Araroba* or *Chrysaroba*, certain powders varying from fine to coarse and from light yellow to dark chocolate, have long been used in Brazil and the East Indies. Formerly supposed to be the product of certain lichens, they are now known to be obtained from irregular interspaces in the wood of the *Andira Araroba*, a large Brazilian tree. Goa powder depends for its activity upon *chrysarobin*. The percentage of chrysarobin in the goa powder varies so much that the crude drug is not recognized in the U. S. Pharmacopœia.

Chrysarobin \* is an odorless, tasteless powder, when first obtained of a pale orange color, but darkening on exposure. It is very slightly

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\* Chrysarobin must not be confounded with *anthrarobin*, a distinct substance produced by Liebermann from alizarin (*Ber. d. Chem. Ges.*, 1888), which Weyl (*Arch. f. d. Ges. Phys.*, 1886, xliii.) has proved to be free from poisonous properties.

soluble in cold water or alcohol, but is freely soluble in alkaline solutions and in hot fats; formerly supposed to be identical with chrysophanic acid, chrysarobin is now known to be a distinct neutral principle. When taken internally in doses of from six to eight grains, it produces in about four hours repeated vomiting, sometimes followed by purging (I. A. Thompson), and it has been shown by Weyl to be an active irritant poison.

Unguentum Chrysarobin (6 per cent.).....External use.

Chrysarobin is never used internally, but as a local application in various skin diseases when there is a tendency to excess of dry exudation, being especially effective in *psoriasis*.

### COUNTER-IRRITANTS.

Almost from time immemorial physicians have believed that morbid processes in deep-seated or superficial organs could be modified by irritations artificially induced in distant parts. To the drugs used for producing these remedial irritations the name of revulsants, or counter-irritants, has been given, the process being called revulsion, or counter-irritation.

The question as to the manner in which a counter-irritant acts is essentially distinct from the question whether it does or does not act. However crude and uncertain our theories may be, clinical experience has demonstrated the value of counter-irritants in various internal conditions. It is proved beyond cavil that internal morbid processes may at times be relieved by creating external irritations.

Our present explanations of the way in which counter-irritants act are certainly not satisfactory. There are abundant physiological proofs demonstrating the connection between distant organs having no apparent anatomical connections; such is the relation between the mammary glands and the uterus; such are the phenomena of so-called metastasis seen in mumps, gout, and other constitutional disorders, in which the development of a new irritation is accompanied by the disappearance of one already existing. Familiar examples, also, may be found in the paraplegias sometimes produced by irritation of a renal calculus, in the headache of gastric irritation, in the shoulder-pain of diseased liver, and in the amaurosis or epileptiform attacks sometimes caused by a decayed tooth. In the well-known experiment of Brown-Séquard it was found that if one sciatic nerve of the guinea-pig be cut epileptic attacks may be produced by gently rubbing the back of the ear upon the same side.

One commonly offered explanation of counter-irritation is that there is only a certain amount of blood in the body, and that if the blood be drawn to one part there must be less in another part. Surely, however, the amount of blood drawn to the skin by a mustard plaster is too small sensibly to affect the general mass in the body. It is more probable that the phenomena of counter-irritation are the



result of reflex disturbances of the vaso-motor nerves which influence the size of the blood-vessels, or of the trophic nerves which directly affect nutrition.

It is of great practical importance to know where the counter-irritant should be placed to affect most powerfully any given internal organ. We have no thoroughly scientific experimental knowledge as to this matter, but it has been clinically demonstrated that the general law for deep-seated parts is that the revulsant should be put directly over the part. When a superficial action is desired, other directions are needed. We are indebted to Anstie for pointing out what appears to be a law, or at least a good working rule for practice,—namely, that when a superficial part supplied by the anterior branches of a spinal nerve is to be affected, the counter-irritant should be placed over the posterior roots of the nerve. Not only can obstinate neuralgia often be relieved by this reflex action, but also the inflammatory changes so often coincident with intercostal neuralgia. The law seems also to apply to cervical nerves, since the proper position for the blister in trigeminal neuralgia is back of the ear or on the nape of the neck.\*

For the purposes of study, counter-irritants are conveniently arranged under two heads: first, those which do not provoke decided alterations of the dermal structure, but simply cause an irritation which soon passes away; these are the *Rubefacients*: second, counter-irritants which produce severe structural alterations. In the latter class belong the hot iron, the issue, the seton, and other destructive appliances, and also the epispastics, vesicatories, or more colloquially blisters, which are used to produce that peculiar inflammation of the cuticle with an outpouring of serum commonly known as the blister.

In choosing between a rubefacient and a blister, the physician is guided by the character of the disease present in the subject. A rubefacient causes a wide-spread, intense but temporary, irritation and congestion of the part,—an irritation which for the moment produces a strong influence, but leaves no permanent impression upon the nutritive acts of the diseased organ. A rubefacient is to be employed when the disease is functional,—when there is only a nervous disturbance or a congestion to be dealt with; whereas the blister is useful when inflammation has produced permanent change. Very frequently in inflammatory conditions, however, rubefacients are useful to relieve accompanying congestion. Thus, in a pneumonia the rubefacient may have no effect upon the focus of the disease, but may be very serviceable in checking a wide-spread collateral congestion.

To the careful use of rubefacients there are scarcely any *contra-indications*; some caution is, however, necessary in their application. A severe internal irritation may so successfully counter-irritate against

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\* The statement of A. Dumontpallier (*Gaz. Hebdomadaire*, November, 1879), that the best results of counter-irritation are obtained by applying the counter-irritant upon the opposite side of the body, so as to be exactly symmetrical with the diseased part, has never to our knowledge been confirmed.

the external counter-irritation that the latter has for the time being no apparent effect, and yet really exerts a disorganizing influence. Thus, a mustard plaster, under the circumstances named, may at the time of its application produce no pain or redness, and yet twenty-four hours afterwards disorganizing inflammation may set in at the seat of the application. When there is severe internal irritation the counter-irritant should always be removed when it has been applied long enough to endanger violent local effects, even though it has exerted no sensible influence.

There is one use of rubefacients which is not that of counter-irritation, but which is often of practical importance. An irritation of the sensitive nerve in the normal animal produces an immediate vaso-motor spasm, and in certain conditions of the body irritation of the mucous membrane or of the skin is of great service in stimulating respiration or circulation. In a true exhaustion rubefacients are of very little value, for the only possible source of absolute increase of power to the system is in food; and in exhaustion those stimulants should be employed which increase the power of assimilating food. For this reason, external irritants are useful as stimulants in conditions of depression rather than of exhaustion. Especially are they valuable when there is wide-spread loss of functional activity in the vaso-motor system. Such conditions of depression, with vaso-motor weakness, exist in *acute collapse* from any cause, in *shock* following injuries, in the first stage of *pernicious malarial fever*, and in other cases when the powers of the system are seemingly overwhelmed by some depressing agency.

Blisters are especially useful in inflammations of serous membranes, such as *pleuritis* and *peritonitis*; are very strongly recommended by some practitioners in parenchymatous inflammations, such as *pneumonia*; and may be of service in persistent forms of nervous irritation, such as the *maniacal delirium* of fevers, when dependent upon the irritant action of a blood-poison, and not upon exhaustion. The amount of serum which is poured out from a blister is sometimes quite large, and vesicants have been even employed to relieve *dropsy*. In general dropsy their use is simply unjustifiable; but in *local dropsies*, as, for example, serous effusion into the pleural sac or into the pericardium, dependent upon local inflammation, they often do good, not only by affecting favorably the disease-process, but also by hastening the removal of the effusion.

In some chronic affections, long-continued severe counter-irritation is required: in such cases a blister may be "kept open" by the use of stimulating ointments, such as the mezereon ointment. In *chronic inflammation* of the *joints*, repeated blistering is very often of service. When the inflammatory action is rheumatic, in our experience better results are obtained by repeated blistering than by keeping a blister sore by means of irritants. In *neuritis*, whether rheumatic or otherwise, blisters are often of service: they should be applied as a long narrow strip along the course of the nerve. In

obstinate local *neuralgia*, very mild blistering over the seat of pain, or in accordance with Anstie's law, is sometimes found to be advantageous.

The *contraindications* to the use of blisters are high arterial and febrile excitement and a decided want of vital power. In the former case, the irritating influence which they exert upon the general system may increase the constitutional disturbance to such an extent as to do more injury than any local benefit derived from them can do good. When the vitality is very low, blisters may give rise to sloughing ulcers, which, refusing to heal, may waste very seriously the already exhausted system. Hence, in all acute diseases of such type that the nutritive forces are exceedingly depressed, blisters must be avoided, or be used only with great caution. For the same reason, great care must be exercised in their employment in the very young or the very aged. Very rarely indeed is a blister called for in the case of a young infant, and if it be employed at all, it should be allowed to remain in contact with the skin only long enough to produce slight pain or redness, and the complete vesication should be obtained by the after-use of a poultice.

The hot iron or other *destructive counter-irritant* is to be used only in cases of continuing chronic disease with structural lesion. At present, neither the moxa nor the issue is ever employed in civilized countries; the seton with extreme rareness. The actual cautery, however, affords a valuable method of treating *chronic neuritis*, *chronic meningitis*, cerebral or spinal, and various forms of *chronic arthritis*.

### EPISPASTICS.

There are various substances which are capable of producing vesication, but the only one in ordinary use is cantharides. In cases of emergency ammonia is sometimes employed. (See page 185.)

### CANTHARIDES.

The dried bodies of the *Cantharis vesicatoria*, a beetle inhabiting Southern Europe. *Spanish flies* are from half an inch to nearly an inch in length and two to three lines in breadth, and have a large heart-shaped head and brilliant metallic-green elytra, or wing-cases. Their odor during life is very strong and fetid, but is almost entirely lost in drying; their taste is urinous, very burning, and acrid. When ground, Spanish flies afford a grayish-brown powder, full of minute greenish spangles, the remains of the feet, head, and wing-cases. The active principle of cantharides is *cantharidin*, which occurs in white crystalline scales, is inodorous, tasteless, insoluble in water, nearly so in cold alcohol; soluble in ether, benzole, the oils, and also very freely so in chloroform. Notwithstanding the insolubility of pure cantharidin, Spanish flies yield their virtues to alcohol and to water.



**Official Preparations :**

Ceratum Cantharidis.....	External use.
Collodium Cantharidatum.....	External use.
Tinctura Cantharidis (10 per cent.).....	1 to 2 minims (0.06–0.12 C.c.).
The plaster although not official is the most popular preparation for external use.	

**Local Action.**—*Absorption and Elimination.*—Cantharides is very irritating, and, when applied to the skin, causes at first redness, with burning, then free vesication and severe pain, and, if the contact be longer maintained, deep inflammation and sloughing. Upon the mucous membranes it produces a no less intense effect. The cantharidin is rapidly absorbed, and is eliminated unchanged by the kidneys.

**Therapeutics.**—Cantharides is employed internally as a stimulant to the genito-urinary organs in chronic inflammation and in *amenorrhœa*. When cantharides is freely used externally as a vesicant there is always some danger of the absorption of a sufficient amount of the active principle for strangury to be induced. The blister should therefore not be left on longer than is absolutely necessary, and in susceptible persons care has to be exercised in its use: whenever active irritation of the kidneys exists, cantharidal blisters should not be applied.\*

**Toxicology.**—Toxic dose of cantharides produces in a few minutes a burning pain in the pharynx, œsophagus, and a sense of stricture in the throat, soon followed by epigastric pain and vomiting, and later, in the majority of cases, by purging. The matters vomited are at first mucus, showing, if the drug has been taken in a powder, little greenish specks through them; then bilious and finally bloody. The stools are mucous, then fibrinous and bloody, often very scanty but excessively numerous and their passage accompanied by great tenesmus. In most cases severe salivation is developed early in the poisoning, frequently accompanied by great swelling of the salivary glands, burning pain in the genito-urinary tract with complete strangury as a characteristic symptom of the poisoning. Aching pain in the back and frequent micturition indicate a commencing uro-genital irritation. These symptoms increase in intensity until there is a constant, irresistible desire to urinate, with violent tenesmus of the bladder, and yet an inability to pass more than a few drops of urine, which is albuminous, and not rarely bloody. In some cases there is a violent erotic excitement, an unquenchable lust, accompanied in man by numerous seminal emissions; † violent priapism, swelling and heat of the organs, and even severe inflammation of the parts may indicate the intensity of the local action of the poison; sometimes gangrene ultimately occurs. Consciousness and general power are often long preserved when the local symptoms and agony are intense,

\* In 1891 Liebreich advocated the use of cantharidin salts in *lupus*, *phthisis* and other forms of tubercular disease. His theory of their action was, however, very improbable, and the method has so entirely failed in practice that it is not necessary here to do more than refer the curious reader to the tenth edition of this treatise for information concerning it.

† Cases, *Journ. de Pharm. et de Chimie*, June, 1871.

but, if the dose have been large enough, sooner or later collapse comes on, with the usual accompaniments, and the prostration deepens into complete powerlessness, stupor, coma, and finally death. In some cases violent hydrophobic delirium and severe tetanic convulsions are said to have occurred (Tardieu). Paraplegia has been noticed in several cases by Pallé: it was probably reflex in its origin, and due to the intense irritation of the genito-urinary organs.

In animals, cantharides produces very much the same symptoms as it does in man. In dogs, according to the experiments of Orfila and of Beaupoil, the symptoms of gastro-intestinal inflammation are more prominent than those of irritation of the genito-urinary tract. It has been asserted that the lack of erotic excitement in these cases shows that the medicine acts differently upon man and upon animals. As already stated, however, erotic delirium is very often absent in fatal poisoning in man, while Schroff states that ten drops of the tincture of cantharides will frequently produce great sexual excitement in man, and the whole drift of the evidence is that libidinous desires are much more likely to be caused by amounts of Spanish flies but slightly toxic than by fatal doses. Indeed, the irritation caused by the latter would seem to be too intense, the general perturbation too great, for erotism to be induced. There appear to be the same differences in the effects of different doses of the drug upon animals. Fatal doses very generally do not excite sexual desire; but Schubarth (quoted by Stillé) found that small doses do cause evident salaciousness and irritation of the genital organs, while, according to Husemann, the peasants of Northern Germany habitually give cantharides to cows when backward in coming into heat at the proper season.

According to Cautieri, toxic doses of cantharides rapidly lessen blood-pressure and the force of the cardiac pulsations, but markedly increase the pulse-rate.

Cautieri found in animals killed with cantharides marked hyperemia of the brain and spinal cord, and nephritis; Gallippe noted inflammation of the alimentary canal, kidneys, and bladder.

The minimum fatal dose of cantharides is not certainly determined, and probably varies very much. According to Stillé, twenty-four grains of the powder, taken in two doses, have caused fatal abortion, and an ounce of the tincture has destroyed life after the lapse of a fortnight. After death, intense injection, swelling, patches of exudation, loss of epithelium, and other results of inflammation are found along the whole tract of the alimentary canal; intense hyperemia of the kidneys, with contraction and congestion of the bladder, also usually exists. According to the experiments of Aufrecht, all the forms of nephritis may be produced by cantharidin, but it is probable that in most cases of poisoning the first change is exudation of the white blood-corpuscles, rapidly followed by a desquamative nephritis, with profound alteration in the glomerules (see Ida Eliaschoff).

There is no known antidote to cantharides, and the treatment of the poisoning must be conducted upon general principles. The stomach should be washed out repeatedly and freely by large draughts of warm water, aided by the stomach-pump or tube, or by a stimulating emetic if the stomach-pump be not at hand. Large quantities of mucilaginous or albuminous drinks should be taken; and all oily substances should be avoided, as favoring the solution, and consequently the absorption, of the poison. Opium should be freely

exhibited, especially by the rectum, to allay pain and relieve the stranguery. For the latter purpose warm sitz-baths or general baths should be employed. In some cases leeches to the epigastrium are advisable. When the suffering is very intense, the cautious use of anesthetics is not only justifiable, but imperative.

**Administration.**—For blistering, the *Cantharides Cerate* is best spread upon sticking-plaster in such a way as to leave a margin about an inch in width, which shall adhere to the skin and hold the plaster in its place. In order for a blister to “draw” thoroughly, it usually has to be left on some eight hours; but in most cases the same result can be achieved with less suffering by allowing the blister to remain only five or six hours, or until decided redness and slight vesication have been induced, and then applying a flaxseed poultice. In certain localities vesication requires a much longer application than that just spoken of; thus, upon the shaved scalp a blister will rarely act efficiently in less than twelve hours, and often not in that time. In maniacs, in the delirious sick, in children, and in other unruly patients it is often necessary to put on a blister in such a way that the sick person has no control over it. For this purpose the *Cantharidal Collodion*\* may be used. It is ordinary collodion impregnated with cantharidin, and on evaporation leaves an adhesive blistering film: two or three coats of it should be applied by means of a camel’s-hair brush. When there is any especial danger to be feared from absorption of the active principle, the use of the poultice, after a brief application of the blister as described above, should always be practised.

## RUBEFACIENTS.

### MUSTARD.

The U. S. Pharmacopœia recognizes two forms of mustard: White mustard (*sinapis alba*), the seeds of *Sinapis alba*, and as black mustard (*sinapis nigra*) the seeds of *Brassica nigra*. Both of these plants are European crucifers cultivated in the temperate regions of the world.

*Black Mustard* yields on distillation a volatile oil, which does not pre-exist in the seeds, but is formed by the decomposition of *sinigrin* or *potassium myronate* in the presence of emulsin. The *volatile oil of mustard* is a colorless or yellowish fluid, of an intensely pungent, or corrosive, odor and taste. A momentary contact with it suffices to redden and blister the skin, and mucous membranes are said to be rapidly destroyed by its vapors.

*White Mustard* contains *sinalbin*, which in the presence of water and emulsin forms *acrinyl sulphocyanate*, an oily, non-volatile, very acrid substance, upon which the activity of white mustard depends.

#### Official Preparations:

Charta Sinapis [Mustard leaves].....	External use.
Oleum Sinapis Volatile.....	External use.

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\* For a case of poisoning by cantharidal collodion, see *Phila. Med. Times*, iv. 312.



**Therapeutics.**—Mustard affords a most excellent material for the practice of mild revulsion. One advantage it possesses is the ease with which it can be controlled. all grades of action, from the mildest impression up to severe blistering, being at the will of the practitioner. It should be remembered, however, that the blister produced by it discharges but little, and is exceedingly sore and painful, as well as very slow and difficult of healing: so that, as an epispastic, mustard is in every way inferior to cantharides, and should not be employed. The black mustard is much stronger than the white, and must usually be diluted at least one-half (by the addition of flour or of flaxseed meal). The white variety may sometimes be employed pure, but generally it also should be reduced in strength.

In many cases it is desirable to maintain for hours a mild, equable counter-irritant impression, and this may be done by adding from one to three teaspoonfuls of mustard, more or less, to a poultice of flaxseed. A mustard poultice (half-and-half black mustard, three parts to one of white mustard and flour) may generally be left on from twenty minutes to half an hour without danger of blistering. Weaker preparations may be used longer.

A mustard plaster may be prepared like an ordinary poultice; but a very convenient method is to take a newspaper folded to a little larger than the desired size, and tear open the front piece so that it can be folded back like a flap, leaving one edge attached; next, to spread upon the thick portion the mustard, leaving the edges free, and then to close the flap upon it and fold the edges back to the desired shape: when done with, this plaster can be thrown away, and no rags are lost. The mustard draws well through the single layer of newspaper covering it, and is, we think, less likely to leave troublesome after-soreness than when employed in the usual manner.

A satisfactory counter-irritant application may also be made by saturating a piece of lint or cotton flannel in a two to four per cent. alcoholic solution of the volatile oil of mustard, applying it in the same way as an ordinary mustard plaster.

**CAPSICUM** and the *stronger spices* afford excellent materials for rubefaction. Cayenne pepper is nearly as strong as mustard, but is much less pleasant to handle, on account of the readiness with which it is diffused, and is much less frequently employed. *Spice-plasters* are useful when it is desired to make a steady, continuous mild impression, as in certain abdominal complaints.

Spice-plasters may be made by the apothecary by means of the following recipe. Take of powdered ginger, ʒii; powdered cloves and cinnamon, each, ʒi; Cayenne pepper, ʒii; tincture of ginger, fʒss; honey, q. s.; mix the powders, add the tincture, and sufficient honey to make of proper consistence for a stiff cataplasma. The domestic spice-plasters are much more elegant and cleanly than those made on the above plan. They are to be prepared as follows. Take equal parts of ground ginger, cloves, cinnamon, and allspice, and one-fourth part of Cayenne pepper, and thoroughly mix them; then put the resulting dry powder into a previously prepared flannel bag of the desired size, distribute the powder equably through the latter, and quilt it in,—i.e., run lines of stitching across the bag, so as to confine the powder in little compartments: when using, moisten thoroughly with common whisky or with alcohol. A plan which has seemed to us still more pleasant is to put two ounces of *unground* ginger, an ounce of unground cloves, cinnamon, and chillies,

or African peppers, in a pint bottle, and pour whisky upon them. After this has stood awhile, the liquor is to be put upon a piece of flannel of the proper size, and the latter is to be laid upon the part and covered with a larger piece of oiled silk, or else a piece of spongiopilin may be employed. If the strength of the preparation is too great, it can readily be reduced by dilution; if it is too little, it can as readily be increased by adding more of the spices, especially of the peppers. In many cases, when the tenderness is very great, the weight of the spice-plaster is objected to. Under these circumstances the substitute here proposed is especially valuable.

### ARNICA.

The *Arnica montana* is a perennial composite, native of Northern Europe and Asia, and said also to be found in the Northwestern United States. The yellow flowers which are the only portion of the plant now recognized have about fourteen striated ligulate tridentate florets in the ray, twice as long as the disk, which consists of numerous tubular florets. Of its two alkaloids, *arnicine* and *cytisine*,\* the latter is said to be identical with the active principle of the laburnum (*Cytisus laburnum*).

**Physiological Action.**—Locally, arnica is stimulating, and, if in sufficient strength, decidedly irritating. Upon some skins the tincture acts even violently, rapidly developing an acute eczematous inflammation of the upper dermal layers, as manifested by hyperemia, papules, vesicles, excoriations, crusts, and scales in regular sequence.

Neither the symptoms of poisoning by arnica nor its physiological action are well made out.

According to H. A. Hare, arnica in dogs increases the activity of the cardio-inhibitory mechanism and also has a slight stimulant influence upon the heart. After large doses the pneumogastric nerves are paralyzed, the arterial pressure remaining near the normal. Stillé has noted the same effects in man, namely, an increase of the cardiac action, and the respiration, elevation of the skin temperature and greater secretion of perspiration and urine. On the other hand, Balding asserts that the drug acts as an arterial depressant.

The symptoms of poisoning seem strangely to vary between those of a violent gastro-intestinal irritant and those of a narcotic poison.

Thus, in a woman, two cups of a strong infusion produced violent gastro-intestinal irritation, as shown by vomiting and choleraic diarrhœa, reduction of the pulse to 60, and finally collapse. In Barbier's case (quoted by Stillé), an infusion of eighty grains of the flowers caused giddiness and intense muscular weakness, with spasmodic movements of the limbs. In another, not fatal, case, according to the statement of the patient, an ounce of the tincture did not produce any symptoms for eight hours, when approaching collapse, dilated, immovable pupils, with a cold, dry skin and a feeble fluttering pulse, rapidly supervened upon an intense epigastric pain, which was increased by pressure. In a not fatal case reported by W. A. Thorn, four hours after ingestion of a fluidounce of a tincture by a young man, the pulse was 100, full and strong, the temperature normal, insensibility complete,

\* J. L. Prevost and Paul Binet find that *cytisine* is a powerful centric emetic, which in large doses paralyzes the motor nerves. Its direct action upon the circulation is very slight; toxic doses cause a gradual lowering of arterial pressure and death by respiratory paralysis (*Revue Méd. de la Suisse Rom.*, vii. and viii., 1887; see also R. Radziwillowicz, *Thesis*, Dorpat, 1887).

conjunctiva anesthetic, respirations 18 per minute, no vomiting or purging. Twelve hours later the patient became wildly delirious; the next day he suffered from burning pain in the abdomen, diarrhœa, and free diuresis.

**Therapeutics.**—In the present state of our knowledge, the internal use of arnica is experimental. Externally it is employed as a stimulant application in *bruises* and *sprains*, generally in the form of tincture (TINCTURA ARNICÆ—twenty per cent.), which may be applied pure. Sometimes fomentations of the flowers are employed. Its property of occasionally producing intense dermal irritation should be borne in mind.

*Burgundy Pitch* was formerly official. It is a concrete juice obtained by wounding the *Abies excelsa*, or Norway spruce,—lofty forest trees of Middle and Northern Europe,—melting the product of the exudation with hot water, and straining. It is hard, opaque, brittle, of a feeble terebinthinate odor and taste, and contains resin and a minute amount of volatile oil. It is a mild rubefacient, which, in the form of plaster, may be kept applied for a long time in *chronic bronchitis* and in *rheumatic affections* of the trunkal muscles. The plaster contains fifteen per cent. of wax. The *Warming Plaster* contains one part of cantharides cerate to twelve parts of Burgundy pitch, and is a very decided counter-irritant whose prolonged use will sometimes blister.

**CARBON DISULPHIDE.**—*Carbon Bisulphide* is a clear, colorless, highly refractive, very volatile liquid, of a strong, disagreeable odor and a sharp aromatic taste. It is very much used in the arts as a solvent, and is an active poison, half an ounce of it having produced death, preceded by coma, with collapse and abolition of reflexes. It has not been used as an internal remedy, but has been employed as a counter-irritant and local anesthetic for the relief of focal, facial, and other *neuralgias*. A small dossil of cotton, saturated with the drug, should be placed on the part and covered with wax paper; or better, a wide-mouthed bottle containing the disulphide and cotton may be inverted upon the part for a few minutes. Even the counter-irritant use of carbon disulphide is not to be encouraged.

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## FAMILY X.—ESCHAROTICS.

ESCHAROTICS are drugs which are used to destroy diseased or sound tissue. Many of them exert a purely chemical influence, while others seem to destroy life by directly affecting the vitality of the part, and are said to act dynamically. Those which act chemically do so in several ways: some, like bromine, probably produce an intense corrosive oxidation, while others, like sulphuric acid, abstract the water.

Escharotics are used for various purposes. Formerly they were employed to open abscesses; but in the very few cases in which the knife is not allowable, aspiration usually affords a superior and safer method. They are constantly applied to destroy unsound, harmful tissues and growths. Thus, they are used to remove the specific tissue of a *chancre*, or to kill a *malignant* or *semi-malignant tumor*. Another purpose which they fulfil is the destruction of *poisoned wounds*. In these cases they may in some instances destroy the poison itself, but at other times they simply prevent the absorption of the toxic agent by putting an end to the life-actions of the tissue containing it. It is hardly necessary to mention all the various cases in which caustics are employed to overcome the effects of poisoned wounds. *Hydrophobia* is a perfectly uncontrollable disease; but the thorough destruction of the wounded tissue at any time before the manifestation of the symptoms will probably prevent its occurrence, as it certainly will if performed early. In *malignant pustule*, life depends upon the free early use of escharotics. Escharotics are employed to produce ulcerations which shall be the bases of *issues*; also, by destroying the exuberant granulations or the indolent surfaces of *ulcers*, to remove at the same time diseased tissue, afford protection to the parts below by forming an impermeable surface, and exert such alterative action upon the part as shall modify for good the life-processes.

It is evident that the choice of the caustic should depend upon the object to be attained. When large tumors are to be killed, or when it is all-important completely to destroy a poisoned wound, a powerful deep-reaching escharotic must be employed; but when the surface of an ulcer is to be filmed over, a caustic which acts superficially and forms a dense albuminous coating, as does silver nitrate, is to be chosen.

An observation of N. A. Randolph and S. G. Dixon indicates that the pain produced by a caustic may be almost nullified by the use of cocaine. They find that the saturated solution of cocaine in nitric

acid acts as powerfully as nitric acid, although much more slowly, and that the only sensation experienced during the production of even a deep eschar is a slight prickling.

All of the more powerful of the escharotics, when taken internally in sufficient amount, act as violent corrosive poisons, producing agonizing pain in the œsophagus and hypogastrium, violent bloody vomiting, often purging of similar character, and finally collapse, deepening into death, which is sometimes preceded by convulsions. When the dose is not so large, the patient may rally from the immediate effects of the poison, to succumb finally to the local lesions produced, or to struggle through a protracted convalescence to health, perhaps only to die years afterwards from organic stricture, caused by the ulcerations of the œsophagus or other digestive tubes. The first indication in poisoning by one of these substances is to neutralize or chemically antidote the poison: with the alkalies, dilute acid, generally convenient in the form of vinegar; with the acids, alkalies, usually at hand in the shape of whitewash or of soap; with other poisons, specific antidotes. Opium should always be freely given, and the symptoms during and after the first poisoning be treated as they arise.

POTASSIUM HYDROXIDE.—When potassium hydroxide is placed upon the skin it soon melts, and, as it does so, gives rise to a pain which increases until it becomes very intense, and continues until the power of the alkali is so diminished that it can no longer reach through the tissue it has killed to the sound flesh below. Under the action of the escharotic the skin becomes of a dirty ashen-gray, and finally a slough is formed, with inflammation of the surrounding parts, and ulceration and detachment of the dead tissue in from six to ten days. The potash appears to act chiefly by abstracting the water, and, to some extent, by combining with the fatty and other portions of the tissues. Its slough being perfectly permeable, and its power being but slowly expended by its own action, potassium hydroxide is one of the most thorough of the escharotics: it is, therefore, to be preferred when a very deep and decided influence is required, as after the *bite* of a *rabid* dog. It is somewhat uncontrollable in its action, and requires care in its use. The best method of application is as follows. Take a piece of thick adhesive plaster, and cut a hole in it of such size that, when the piece is warmed and properly placed upon the skin, the part to be acted upon will be exposed while all around it will be protected. Then apply the plaster, and grease the outer surface of it, without allowing any of the oil to come in contact with the exposed central skin. Then lay the caustic potash upon the latter, and, when the action is believed to have extended deep enough, wash the part with dilute vinegar.

VIENNA PASTE, a grayish-white powder, composed of equal amounts of potassium hydroxide and caustic—*i.e.*, unslacked—lime.

It is not so active as caustic potash, but is less likely to spread and diffuse itself. It is to be mixed with sufficient alcohol to form a paste, and then applied like caustic potash.

Piedagnel affirms that this caustic may be rendered nearly or entirely painless by mixing one part of morphine hydrochloride with three parts of the powder, and then by the addition of chloroform forming a paste that may be spread upon lead plaster and so applied. In five minutes the skin under the application becomes of a dead-white color, and at the end of fifteen minutes is brown and carbonized. If the application be persisted in, the thickness of the eschar will become finally about equal to that of the layer of the paste employed. Cocaine would probably be more efficient in preventing pain than the morphine.

**ARSENIC TRIOXIDE.**—As a caustic, arsenic is energetic and powerful, but somewhat slow, and causes intense pain, with violent inflammation of the neighboring parts. It is stated to affect more rapidly morbid than normal structures, and is especially used for the destruction of malignant growths. It appears to act chiefly upon the vitality of the part, acting, when sufficiently diluted, as a powerful irritant, and when in a concentrated form producing an irritation so intense that life cannot endure it. Hence, probably, the reason of its affecting more rapidly morbid growths, which have a lower vitality than sound tissues.

The great objection to the employment of arsenic is the possibility of its absorption in sufficient amount to cause constitutional symptoms: even death has resulted from its external use. Since absorption takes place much more rapidly in a healthy than in an intensely inflamed or a dead tissue, whenever arsenic is employed as a caustic it should be used so freely as to kill the tissues rapidly, and under *no* circumstances should it be applied to a fresh wound. Used in any way, arsenic is a hazardous caustic, and it ought to be employed only with the knowledge and distinct remembrance of this fact. *Cancer*, and perhaps some forms of semi-malignant ulceration, such as *lupus*, appear to be the only diseases which justify its use.

There is no reason for believing that any of the almost innumerable substances which have been proposed as a basis for arsenous pastes possess peculiar advantages: the only needful direction is to mix the caustic with from eight to ten times its bulk of inert material of such a nature as to make either an ointment or a paste, and to allow this to remain on the part for from eighteen to twenty-four hours.

**ZINC CHLORIDE.**—Zinc Chloride occurs in broken fragments of a grayish-white color, or as a white or nearly white granular powder, translucent and waxy in appearance, of an acrid corrosive, or, when diluted, acrid astringent, metallic taste. It is extremely deliquescent, fusible, volatilizable at a high temperature, and very soluble in both water and alcohol. Zinc chloride is a very powerful caustic, producing, when applied in a concentrated form, intense pain lasting from six to eight hours, and a whitish eschar, which usually separates in from six to twelve days. Its penetrating powers are a little less,



and its action more readily controlled, than is that of potash; its absorption does not endanger life, as is the case with arsenic trioxide; and it leaves a slough which is free from odor.

*Canquoin's Paste* is made by mixing zinc chloride with flour and water. The strength varies according to the purpose, the weakest paste containing only one part of the caustic in six parts; the strongest, one part in three. When used, ten or fifteen drops of water are added to the paste, which is applied in layers, successive applications being required when a large tumor is to be destroyed. Anhydrous calcium sulphate has been especially commended by A. Ure, as forming a drier paste with the escharotic and limiting its action more definitely to the site of application than any other substance. Concentrated alcoholic or aqueous solutions of zinc chloride are often used as caustics in cases of *chancres* and other small *specific ulcers*, and are reputed to be efficient. They should be applied by means of little pledgets of lint. As the action of the chloride upon the skin is slow and very painful, whenever the cuticle over the part to be destroyed is sound it should be removed by means of blisters. By some surgeons the escharotic is introduced directly into the tumor to be destroyed. The official solution (*LIQUOR ZINCI CHLORIDI*) has been used as a disinfectant, but is of very little value.

**MERCURY BICHLORIDE.**—*Corrosive Sublimate* is an escharotic of moderate power, which shares the dangers of arsenic, since death has followed its external use. In saturated solution it is much used as a caustic in *chancres*, but is scarcely equal to the solution of mercuric nitrate. In these cases it should be applied by means of a camel's-hair brush. The late George B. Wood recommended very highly that in *onychia maligna* a powder composed of equal parts of corrosive sublimate and zinc sulphate intimately mixed should be sprinkled thickly over the diseased surface, and a pledget of lint thoroughly wet with laudanum laid thereon. There is severe pain for half an hour to an hour; but the dressings are not to be removed until eight or ten hours have elapsed. When the slough which is thus formed separates, a healthy granulating surface is left.

**MERCURIC NITRATE.**—The solution of Mercuric Nitrate (*Liquor Hydrargyri Nitratis*) is a nearly colorless, highly corrosive, acid liquid, having a specific gravity of 2.086, and made by dissolving mercury, or its red oxide, in a large excess of nitric acid. Its application to a space not bigger than a half-dollar has produced very serious poisoning.\* It is rarely used, except for the purpose of destroying *specific* or *cancerous ulcers*. It is especially useful in *chancres*, to which it should be applied with a glass rod. In obstinate *acne*, an indolent tubercle may be destroyed by a minute drop without producing a scar. It has been largely employed by gynecologists

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\* Case, *Lancet*, January 3, 1874.

in *ulcerations of the cervix uteri*. Its action is very prompt and is moderately deep; the pain is severe, but transient.

NITRIC ACID is a powerful caustic, which is never employed to destroy large tumors, but is a favorite application to *chancres*, to *syphilitic*, *phagedenic*, and other unhealthy *ulcers*, and to *condylomata* and other small *dermal growths*. A drop or two may be applied by means of a glass rod or a wood splinter, and when the action has gone far enough, neutralized with sodium carbonate or soapsuds.

CHROMIUM TRIOXIDE.—*Chromii Trioxidum*, commonly known as *Chromic Acid*, occurs in anhydrous acicular crystals, of a deep purplish-red color, and an acid, metallic, corrosive taste. They are very deliquescent, melting down, when exposed to the air, into an orange-red solution. Chromium trioxide is a very active oxidizer, and when mixed with organic matter rapidly alters it, and if in slight excess will dissolve almost any form of tissue. It is used to destroy *condylomata* and other *dermal growths*, and is best applied by means of a glass rod, the liquid formed by the spontaneous deliquescence of the crystals being used. Chromic acid is sometimes prescribed, dissolved in or made into a paste with glycerin, but it is stated that in mixing the two great care must be taken to add the liquid slowly, drop by drop, as otherwise there is danger of an explosion. In the German army, painting the soles of the feet and the skin between the toes with a five-per-cent. solution of chromic acid is said to have had a very great influence in increasing the marching powers of the troops, by arresting excessive sweating, and hardening the skin. Chromic acid is a violent corrosive poison, a single drop of the saturated solution having caused very severe symptoms.\* The nature of the poison may often be recognized by the reddish-brown, or more rarely greenish, discoloration of the skin of the lips and of the mucous membrane of the mouth and gullet, but this discoloration may be absent. In a number of cases death has resulted from the too free external use of the acid.†

TRICHLORACETIC ACID.—*Acidum Trichloraceticum* occurs in deliquescent crystals. It has been used to a considerable extent for the destruction of papilloma and other growths; a single crystal placed on a growth produces immediately a white, dry, adherent mass, which falls off in a few days. The pain is said to be not at all severe, and may be entirely prevented by the use of cocaine.

BROMINE is a dark brownish-red liquid which has a very powerful, disagreeable, chlorine-like odor, and at ordinary temperatures emits exceedingly acrid, pungent fumes. It is sparingly soluble in water, more soluble in alcohol, and still more so in ether. When

\* Case, *Brit. Med. Journ.*, 1889, i.

† For experiments as to its effects on animals, see *A. E. P. P.*, vi.; also *Stricker's Jahrb.*, 1877, 139. For cases of poisoning, see *S. J.*, 1884, cci. 129; *U. M. M.*, ii.; *M. M. W.*, 1903, i. 691; *D. A. K. M.*, lxxv.

brought into contact with organic matter, it oxidizes and completely destroys it with great rapidity. On account of this property and of its liquid form, bromine is one of the most severe, thorough, and rapid of all the caustics. It has not been much employed to destroy morbid growths, but has been found very efficient in *hospital gangrene*. After most of the slough has been cut away, the caustic should be applied pretty freely to the living tissue by means of a glass rod. When taken internally, bromine acts as a very powerful corrosive poison.\*

*Zinc Sulphate*, *Copper Sulphate*, and *Burnt Alum* are feeble escharotics, used only to destroy *exuberant granulations* in ulcers.

**PYROGALLOL.**—*Pyrogallic Acid* is a triatomic phenol which may be prepared synthetically, but is usually obtained, in accordance with the directions in the U. S. Pharmacopœia, as the result of the igneous decomposition of gallic acid. In concentrated form it is a powerful caustic, and as such, and also in the form of dilute ointment or solution, five to forty grains to the ounce, has been considerably used in the treatment of *lupus*, *psoriasis*, and allied affections of the skin. It is a violent poison, and in various cases death has followed its too free external use. Half an ounce of it, taken internally, has produced death in four days. The symptoms which follow its external use have been malaise, vomiting, diarrhœa, headache, pallid and cyanosed lips, collapse, a peculiar greenish hue of the skin, rapid pulse and respiration, albuminous urine, becoming dark brown or black from the presence of methemoglobin, icterus, insomnia, restlessness with diminished reflexes, and death preceded by delirium, convulsions, and coma. In pregnant women abortion without death of the mother has occurred as the result of the external use of the ten-per-cent. ointment of the pyrogallol, in psoriasis (Busch). When the poison has been due to the internal use, violent burning pains, black vomit, and other evidences of its irritation to the gastro-intestinal tract are usually present. As noted by Personne, these symptoms resemble those of phosphorus-poisoning, and wide-spread fatty degeneration and other post-mortem lesions similar to those caused by phosphorus are found after death.

**LACTIC ACID.**—Under the title of *Acidum Lacticum* the U. S. Pharmacopœia recognizes a preparation containing seventy-five per cent. of absolute lactic acid. The suggested use of this remedy, as a hypnotic, has passed into a deserved desuetude. The only practical use to-day of lactic acid, is as a caustic in laryngeal and dermal *tuberculosis* and similar ulcerative conditions.

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\* For cases, see *Schmidt's Jahrb.*, cxxxi.; also *Vierteljahr. f. Gerichtl. Med.*, 1889.



## FAMILY XI.—DEMULCENTS.

THESE are bland substances, which form more or less gummy or mucilaginous solutions in water, capable of exerting a calming or soothing influence upon inflamed surfaces. Their action is probably purely mechanical, their adhesiveness causing the water they are in to remain long upon the part; they are, as it were, vehicles for water, the demulcent *par excellence*. It has been affirmed not only that demulcents soothe surfaces to which they are immediately applied, but also that taken internally they relieve irritation in distant organs. There is, however, no reason for supposing that such of them as escape digestion are absorbed or yield to absorption any principles in sufficient quantity to exert an influence upon the general system. The relief which undoubtedly follows their use in certain affections of parts which they can reach only through the circulation is probably due to the large quantities of water with which they are administered, lessening the concentration, and hence the acidity, of the urine and other secretions.

Clinically, demulcents are useful as local applications in all forms of acutely inflamed surfaces, and they are taken internally in acute *inflammatory* conditions of the *alimentary canal*. In slight *bronchial irritation* they are often of service, especially when allowed to dissolve slowly in the mouth: used in this manner, they not only exert an influence upon the mucous membrane of the mouth, but very probably find their way also into the respiratory passages.

### ACACIA.

*Gum Arabic* is a gummy exudation from *Acacia Senegal*, and other species of *Acacia*, small trees growing in Northern Africa, Senegambia, Guinea, etc., the Cape Colony, and Australia. Gum arabic occurs in roundish or irregular pieces, more or less transparent, hard, brittle, varying in color from white or yellowish white to red, or even deep orange brown. It consists of a peculiar, feebly acid, amorphous principle, *Arabin*, united with about three per cent. of lime, potassium, and magnesium oxide. In the plant, arabin, like other gums, appears to be formed by a retrograde metamorphosis of cellulose. On account of its solubility in water and pleasant taste, gum arabic is often used as a demulcent in *irritation of the fauces* and in *angina*. It is sometimes employed as an addition to drinking-water in fevers, and is believed to have slightly nutritious properties. Its chief use, however, is in Pharmacy, in the making of emulsions, pills, etc.

**Official Preparations :**

Mucilago Acaciæ.....	Vehicle.
Syrupus Acaciæ.....	Vehicle.

TRAGACANTH (*Tragacantha*) is the concrete juice of *Astragalus gummifer*, and of other species of *Astragalus*, a small shrub of Asia Minor. Tragacanth occurs in large, whitish, horny, waved flakes, or sometimes in filamentous pieces. It is odorless and nearly tasteless. Introduced into water it does not dissolve, but swells up into a soft paste. One hundred parts of it contain, according to Guérin, 53.3 parts of arabin, 33.1 parts of bassorin, and 2.5 parts of inorganic ash. *Bassorin* is a gummy principle, at once distinguished from arabin by its not dissolving in water, but simply swelling up into a pasty mass. Tragacanth is used only in the manufacture of troches and in suspending heavy powders, for which purpose the difficulty of its solution and the extreme viscosity of its mucilage especially fit it. Its mucilage (MUCILAGO TRAGACANTHÆ) is used in varying dose as a vehicle.

ULMUS.—*Slippery Elm* is the inner bark of *Ulmus fulva*, a large indigenous tree. The bark is of a yellowish-white or tan color, fibrous, yet when dry somewhat brittle, and occurs in long, flat strips or pieces one or two lines thick. It is pleasantly mucilaginous when chewed. It contains a large quantity of a peculiar mucilage, which it yields freely to water. Its infusion is sometimes taken in large quantities in *inflammations of the intestines*, as a demulcent laxative; but its chief use is as an external application. When ground into powder, slippery elm makes an excellent soothing poultice. The mucilage (MUCILAGO ULMI) is used in varying dose as a vehicle.

CHONDRUS.—*Irish Moss*, or *Carrageen*.—The fronds of *Chondrus crispus*, a sea-weed growing on the coast of Ireland, and also on the northern coast of the United States, where it is now gathered in large quantities. The fronds are purplish red,—but, as kept in the shops, bleached by washing in fresh water, whitish and translucent,—cartilaginous, slender, much branched, swelling up but not dissolving in water, and having a slightly saline taste. Their virtue depends chiefly upon a starch- or gum-like principle, *Carrageenin*, which is distinguished from starch by not turning blue with iodine, and from gum by not precipitating from its watery solution on the addition of alcohol. Chondrus also contains a notable proportion of a vegetable albumen.

Carrageen, being demulcent and nutritious, is employed as an article of diet in those cases requiring food of such character, and may be used instead of arrow-root. It is to be prepared by first soaking for ten minutes in cold water, and then boiling from half an ounce to an ounce of it (according to the desired consistency) in a pint and a half of water down to a pint, sweetening and flavoring to taste. Milk may be substituted for water.

**GLYCYRRHIZA.**—*Licorice Root* is the root of *Glycyrrhiza glabra* and *glandulifera*, native herbs of Southern Europe. It occurs in long, cylindrical pieces, from a few lines to more than an inch in diameter, brownish externally and yellowish within. Its fracture is fibrous, its taste sweet and mucilaginous, its odor none. Its active principle is *Glycyrrhizin*. This is a sweet, neutral substance, differing from the sugars in not being converted by nitric acid into oxalic acid, and by its inability to undergo the vinous fermentation.

#### Official Preparations :

Extractum Glycyrrhizæ [Licorice]. . . . .	Vehicle.
Extractum Glycyrrhizæ Purum. . . . .	Vehicle.
Glycyrrhizinum Ammoniatum. . . . .	5 to 10 grains (0.3–0.6 Gm.).
Fluidextractum Glycyrrhizæ. . . . .	Vehicle.
Elixir Adjuvans. . . . .	Vehicle.
Mistura Glycyrrhizæ Composita [Brown Mixture] (Licorice 3, Camphorated Tincture of Opium 12, Wine of Antimony 6, Spirit of Nitrous Ether 3 per cent.). . . . .	$\frac{1}{2}$ to 1 fluidounce (15–30 C.c.).
Trochisci Glycyrrhizæ et Opii (Each contains $\frac{1}{32}$ grain (0.005 Gm.) Opium). . . . .	

Licorice root is very largely used as a demulcent in pectoral complaints, and, on account of its pleasant taste, as a means of disguising or of flavoring medicines. In the form of glycyrrhizin it is said to conceal almost entirely the bitter taste of quinine and similar substances. It is used almost exclusively in the form of the extract, known as *Licorice*. The compound mixture of glycyrrhiza is much used as a domestic remedy in *colds* and the early stages of *mild bronchitis*. The ammoniated glycyrrhizin is an elegant demulcent preparation which, however, is incompatible with acid or alkaline solutions.

**LINSEED** or **FLAX-SEED** is the seed of *Linum usitatissimum*, or common flax, and contains large quantities of mucilage and of oil; its infusion, *Flax-seed tea*, is much used internally. It is often made with boiling water; but the application of too much heat causes the extraction of the oil, and renders the preparation less palatable. The addition of lemon and sugar makes it more palatable. It may be drunk *ad libitum* in pectoral *catarrhs*, in *enteritis* and *dysentery*, and in *irritation* of the *kidneys* or the *urinary passages*.

**STARCH.**—Obtained from Indian corn, a white, inodorous, tasteless powder, composed of microscopic granules, is physiologically inert except as a food. It is often used as a dusting powder in irritant conditions of the skin; as a soothing demulcent in the preparation of opiates and other rectal injections, and pharmaceutically for the purpose of thickening or gelatinizing ointments, and the making of paste for use in skin diseases.

**MEDULLA SASSAFRAS**, or *Sassafras Pith*, yields a delicate mucilage much used in eye diseases (**MUCILAGO SASSAFRAS MEDULLÆ**, U. S.).



**ALTHÆA.**—The roots of *Althæa officinalis* yield a bland mucilage; their decoction is sometimes given in gastric irritation, and their syrup (*Syrupus Althææ*, U. S. 1890) is used as a vehicle.

**CETRARIA.**—*Iceland Moss* is the fronds of a lichen, *Cetraria islandica*, growing on rocks in Iceland and in most of the northern portions of the world. It is said to be abundant in the mountains of New England. The foliaceous, dry, shining, lobed, and lacinated fronds are about four inches long, of various intermixed colors, gray, brown, and red, and of a mucilaginous, bitter taste. Iceland moss contains a peculiar lichen starch and a bitter principle. It yields to cold water its bitterness; to boiling water all of its virtues. *Cetrarin*, or *Cetraric Acid*, is the bitter principle, which may be obtained as a snow-white mass of interlaced acicular crystals. It unites with alkalies to form salts. With it in the lichen is associated in small quantities *lichenstearic acid*. Kobert has found that cetrarin has no effect upon the arterial pressure; also that in toxic dose it produces violent convulsions in the cat and in the dog, while in small dose it distinctly increases the activity of the motor area of the brain and spinal cord. Kobert also asserts that in healthy men cetrarin increases the number of the red and, in a still greater degree, of the white corpuscles; and believes that in *chlorosis* and *anemia*, especially when there is constipation, cetrarin will prove a valuable remedy.

*Lichenin*, or *Lichen Starch*, the mucilaginous, nutritive principle of Iceland moss, differs from ordinary starch in not being deposited in granules within the cells, but in layers or irregular masses between the cells, or indeed forming the walls of the cells (De Bary). In cold water it swells up without dissolving; in hot water it dissolves, and on cooling condenses into a jelly. With iodine it strikes a yellow, green, or sometimes rather faint blue, color. It is found in very many lichens; also in many species of sea-weed, notably in the so-called *Corsican moss*.

Iceland moss has enjoyed some reputation as a demulcent in pectoral complaints. From its bitter principle, it is somewhat tonic, and its lichenin is probably about equal to ordinary starch as a nutrient. When prepared as an article of diet, in the form of jelly, the bitter taste should be removed by soaking for some hours in a very weak, cold alkaline solution, and afterwards for a little while in cold water.

**HORDEUM.**—The decorticated seeds of the common barley constitute the *pearl barley* of commerce. They contain starch and mucilage, and the decoction was formerly official. *Barley water* is used as a nutritious, demulcent drink in fevers and inflammatory conditions, especially when the gastric mucous membrane is involved. The U. S. Pharmacopœia of 1870 directed that it should be prepared as follows: "Take of barley two troy ounces; water a sufficient quantity. Having washed away the extraneous matters which adhere to the barley, boil it with half a pint of water for a short time and throw away the resulting liquid. Then, having poured on it four pints of boiling water, boil down to two pints, and strain."

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## FAMILY XII.—EMOLLIENTS.

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TRUE emollients are perfectly bland, fatty substances, which, when applied to the skin, soften it and render it more pliable. The action of these remedies is largely mechanical, and they probably soften the derm in precisely the same way as they affect a raw hide or a piece of leather. They are therefore especially useful when the skin has a tendency to crack or to chap. Whenever surfaces become sore by attrition, or, in other words, chafe, emollients are also useful mechanically. They often afford relief in simple inflammations of the skin under such circumstances that their action cannot be explained as purely mechanical: indeed, they seem to exert a dynamic influence upon the nutrition of the parts concerned. It may be that they shut out or interfere with the development of pathogenetic germs, or, in other words, that they are mechanical antiseptics. Be these things as they may, clinical experience has demonstrated that fatty matters are of very great value in the treatment of superficial inflammations.

The blandest fat, when it becomes rancid, is very irritating, and will do more harm than good, so that the strictest attention must be paid to the condition of the fatty material employed. Any perfectly bland oily substance may be used as an emollient.

The fatty bases are also used largely as a means of introducing drugs into the general system. This, the so-called endemic method of administering remedies, is used especially for drugs which are likely to irritate the gastro-intestinal tract. The disadvantages of this channel of absorption are its slowness and the uncertainty of dosage. There does not appear to be any marked difference in the power of true fats in penetrating the skin, excepting in so far that a hard fat does not readily melt at the temperature of the body, and therefore does not yield itself to absorption so readily as does a soft one. The petrolatums, however, are not at all fitted for ointment bases when systemic effects are desired.

The fats are combinations of either oleic, palmitic, stearic acid or allied substances with glycerol. Most fats contain more than one of the fatty acids. The consistence depends upon the relative proportions of the various fatty acids. The most fluid of the ordinary fats is olein, and the most solid is palmitin, stearin occupying a position midway between them.

There are certain substances, as petrolatum and glycerol, which while not fats, in the proper sense of the word, have similar emollient virtues and are therefore considered in this family.

**Official Fats and Ointment Bases :**

Official Name.	Common Name.	Consistency.	Congealing or Melting Point.
Acidum Oleicum	Oleic Acid	Liquid	39.2° F.
Acidum Stearicum	Stearic Acid	Solid	133°-156° F.
Adeps	Lard	Soft	100.4°-104° F.
Adeps Benzoinatus	Benzoinated Lard	Soft	
Adeps Lanæ	Wool-fat	Soft	104° F.
Adeps Lanæ Hydrosus	Lanolin	Soft	104° F.
Cetaceum	Spermaceti	Solid	113°-122° F.
Sevum Præparatum	Mutton-suet	Solid	113°-122° F.
Cera Alba	White Bees-wax	Solid	147°-149° F.
Cera Flava	Yellow Bees-wax	Solid	144°-147° F.
Oleum Adipis	Lard Oil	Liquid	32° F.
Oleum Amygdalæ Expressum	Oil of Sweet Almond	Liquid	-4° F.
Oleum Gossypii Seminis	Cotton Seed Oil	Liquid	23°-32° F.
Oleum Lini	Linseed Oil	Liquid	-4° F.
Oleum Olivæ	Olive Oil	Liquid	32° F.
Oleum Ricini	Castor Oil	Liquid	0° F.
Oleum Theobromatis	Cocoa-butter	Solid	86°-95° F.
Glycerinum	Glycerin, Glycerol	Liquid	
Paraffinum	Paraffin	Solid	125°-135° F.
Petrolatum	Vaseline	Soft	113°-118° F.
Petrolatum Album	White Vaseline	Soft	113°-118° F.
Petrolatum Liquidum	Albolene	Liquid	

**Official Mixed Ointment Bases :**

Ceratum.....	White Wax 30, White Petrolatum 20, Benzoinated Lard 50 per cent.
Unguentum.....	White Wax 20, Benzoinated Lard 80 per cent.
Unguentum Aquæ Rosæ....	Spermaceti 12.5, White Wax 12, Expressed Oil of Almond 56, Sodium Borate 0.5, Stronger Rose Water 19 per cent.
Glyceritum Amyli.....	Starch 10, Water 10, Glycerin 80 per cent.

OLIVE OIL is the ordinary salad oil of the table, and may be used wherever a very bland oil is desired. It has, however, no superiority for ordinary purposes over the *Cotton-seed Oil*, indeed, a very large proportion of the olive oil of commerce is cotton-seed oil; it is credibly affirmed that more cotton-seed oil is exported from New Orleans to the Mediterranean cities than olive oil is exported from those ports, much of the cotton-seed oil coming back with olive oil labels. There seems to be no sufficient reason for believing that olive oil differs from cotton-seed oil in its physiological or therapeutic properties. These oils are sometimes used internally with advantage, for nutritive purposes, and are also very mildly laxative. The assertion, originally made by Kennedy, that large doses of olive oil are very useful against *biliary calculi*, has received strong clinical confirmation. S. Rosenberg found that in dogs with biliary fistulæ olive oil not only increased the amount of bile, but also rendered the bile much more liquid. Since fats are absorbed chiefly, if not entirely, through the thoracic duct, it would appear that the oil must pass through the pulmonary circulation before reaching the liver. This is confirmed by the experiments of Chauffard, who could not find in the bile-



duet or gall-bladder any trace of oil which he had injected into the stomach of the dog. If olive oil has the asserted remedial influence, it probably acts reflexly through the nervous system,—through a mechanism provided by nature for the purpose of aiding in the digestion of fats when in excess. The dose of the oil should be not less than from five to seven fluidounces (150–215 C.c.) taken in four to eight portions in not longer than three hours. It may be given in aromatized emulsion, with a little brandy or whisky if desired.

**OIL OF THEOBROMA** on account of its firm consistency and comparatively low melting point is largely used for making suppositories and bougies.

**WOOL-FAT** is obtained from the wool of sheep, which is said to contain, on an average, forty-five per cent. of it. It appears to be practically the same as the natural oil of the hair in man and other animals.\* The **HYDROUS WOOL-FAT** contains about thirty per cent. of water, and is the form of the unguent ordinarily employed. It was first recommended by Oscar Liebreich as a basis for ointments or preparations to be applied to the surface of the skin. It is entirely free from irritant properties, has the power of taking up a large amount of water without losing its unctuousness and does not easily become rancid; it has been asserted that it is absorbed through the skin much more readily than are other fats. In the experiments of Patschkowsky, half an hour after inunction with lanolin and potassium iodide the iodine was recognized from the urine, while official potassium iodide ointment yielded negative results. This has been confirmed by Kaspar, but Ritter and Pfeiffer obtained contrary results, and in a considerable series of experiments were unable to perceive that lanolin had any superiority over other fats in promoting absorption. The facts, moreover, that lanolin is largely the secretion of sebaceous follicles, contains an abundance of cholesterin, and is in the nature of a waste product which is intended, not for absorption but for the keeping soft of the skin and its appendages, indicate very strongly that it will yield itself, and medicinal substances with which it may be impregnated, *less* readily to absorption than do other fats. As a basis of ointments used to medicate the skin it is most effective, but when absorption is desired it is probably inferior as a vehicle to ordinary fats.

**PETROLATUM.**—The solid basis of petroleum is paraffin, and after the distillation of the more volatile portions of the petroleum there are left mixtures sold as vaseline, cosmoline, etc., whose consistency varies in proportion to the amount of the liquid hydrocarbon left in them. Of this class are paraffin and the various forms of petrolatum recognized by the Pharmacopœia. They are all insoluble in water, do not become rancid, are free from irritating properties, and act

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\* See *Virchow's Archiv*, 1890, cxxi.

mechanically on the skin like fats. They are used as local emollient applications to the skin and mucous membranes and as a basis for ointments. When taken internally in the dose of a drachm to an ounce they exert no influence upon the system, but act locally upon the mucous membrane of the alimentary canal, allaying irritation and provoking soft fecal discharges.

### GLYCEROL.

*Glycerin* is a thick, syrupy liquid, colorless, free from odor, and of a sweet taste. Chemically speaking, it is *propenyl alcohol* and is, therefore, more correctly called glycerol. It is always set free during the process of saponification, and formerly was a by-product in the manufacture of soaps. At present it is made by the direct decomposition of fats by superheated steam.

Under certain circumstances, not well understood, glycerin forms hard, brilliant crystals. In its usual liquid form it mixes in all proportions with water and alcohol, and itself dissolves iodine, bromine, tannic and other vegetable acids, a large number of salts, and various organic principles. It throws, however, most alkaloidal salts out of their aqueous solution.

Glycerin does not evaporate upon exposure, but is very hygroscopic, and absorbs water from the air. When pure, it is incapable of becoming rancid or of fermenting spontaneously. The acrid glycerin owes its irritant properties to impurities, especially to oxalic and formic acids; cheap grades of glycerin are frequently contaminated with arsenic.

**Physiological Action.**—When large doses of glycerin (in the dog eight or more parts per thousand by weight) are injected subcutaneously, death is produced in a period varying, according to the dose, from one hour to several days. The symptoms are loss of muscular strength, lethargy, bloody urine, vomiting, dryness of the mucous membrane, with marked thirst, fall of temperature, gradual extinction of both respiration and circulation, and finally convulsions and coma (Dujardin-Beaumetz and Audijé). The convulsions occur earlier and are more severe when large doses are employed, and are then said to be tetanic, and to be accompanied by a decided rise of temperature. The fall of temperature is, even in the milder cases, present only late in the poisoning, and is sometimes, if not always, preceded by a rise. After death intense congestion, with more or less softening of the tissue, is found in the lungs, kidneys, and intestines. So far as we know, the largest amounts of glycerin taken by the stomach in man have produced no other symptoms than those of mild gastro-intestinal irritation; but Schellenberg has reported a long series of cases in which serious, and in one instance fatal, poisoning followed the injection of glycerin containing iodoform, for coxitis and other diseases. The conclusion of Schellenberg, that the manifestations were due to the glycerin, is confirmed by the fact

that they were those seen in the lower animals poisoned by injections of glycerin,—namely, loss of muscular strength, elevation of temperature, rapid pulse, albuminous bloody urine with tube-casts, and in the fatal case the lesion of acute parenchymatous nephritis.

Catillon asserts that glycerin administered in small continuous doses exerts a decided effect upon nutrition, but the general drift of the present evidence is to show that glycerin has no distinct effect upon tissue-changes.

In Catillon's experiments, eight grains given daily to guinea-pigs caused a very marked gain in weight, with a lessened excretion of urea. In man an ounce daily also produced a decided diminution in the elimination of urea, which was not increased by increasing the doses of glycerin. The appetite in many cases was, after a little time, much improved, and then the increased ingestion of food produced an increased elimination of urea. The fact that an increase of food was permitted in these experiments shows, however, that the conditions of experimentation were not rigid enough to allow much weight to be attached to the result; and the relation of glycerin to the elimination of urea has been investigated by L. Lewin, by N. Tschirwinsky, and by I. Munk, with somewhat contradictory results. Of these experiments the most extensive are those of Munk, who seems to have used all proper precautions, and who found that glycerin has no effect upon the elimination of urea or upon the general bodily nutrition. The results reached by Lewin correspond with those of Munk. Tschirwinsky omitted fatty materials from the food, and found that while at first the elimination of urea was diminished, it afterwards, under the use of very large doses of glycerin, was increased.

Glycerin is absorbed from the alimentary canal, and when freely administered is in part eliminated and in part burnt up in the system.

Both Ustimowitsch and Plósz found a substance in the urine which they believe to be a derivative product of glycerin, while Catillon proved that it is not eliminated by the skin or, even when it purges, by the intestines. Catillon and Lewin recovered from the urine only a small proportion of that ingested, Tschirwinsky only 8.7 per cent., while Ludwig Arnschink found that not more than thirty per cent. escapes from the body. Since a large proportion of ingested glycerin is oxidized in the body, it would appear that it is capable of replacing to some extent true fatty carbohydrates for the production of heat or energy, and, therefore, has food value. According to the calculations of Arnschink, two hundred and nineteen parts of it are equivalent to about one hundred parts of fat. This view is corroborated by the work of Scheremetjewsky, who found in rabbits that the intravenous injection of glycerin was followed by an immediate increase of the consumption of oxygen, and of the giving up of carbonic acid.

The work of Scheremetjewsky has given rise to considerable controversy, but the latest experiments, those of I. Munk, seem to lead to the conclusion that glycerin is capable of taking the place of the bodily fat.\*

According to Fuchsinger, the bloody urine produced by poisonous doses of glycerin contains an abundance of the coloring-matter of the blood, but no free corpuscles. Very interesting in connection with the use of glycerin in diabetes is the assertion of Fuchsinger, that in rabbits slightly poisoned with glycerin no sugar appears in

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\* For discussion, see *Archiv f. d. Ges. Phys.*, 1889-90, xlvii.



the urine after the "diabetic puncture." The experiments of Eckhard gave, however, a contrary result, and Catillon affirms that given in very large continuous doses glycerin increases the amount of sugar in the blood.

**Therapeutics.**—Locally applied, glycerin is usually unirritating, and it is much employed as an emollient. The chief disadvantage that attends its use is its stickiness; on the other hand, its non-volatility and its hygroscopic properties give a persistency to its action which is often very advantageous. It enters largely into the composition of popular emollient ointments, or "creams," as they are called, and is often used itself for *chapped hands*, *excoriations*, and similar troubles. It is also employed by dermatologists to some extent in *chronic eczema*; in *seborrhœa*, whether affecting the hairy scalp or other parts, it is asserted to be especially useful, softening the masses of secretion, and, used in conjunction with such remedies as borax, zinc, and lead acetate, diminishing the amount of secretion. When there is a want of sebaceous secretion, it is said also to act efficiently; in *scabies*, *pruritus*, and even *psoriasis*, glycerin is used, diluted with water, as a vehicle for more active remedies. Upon the mucous membranes glycerin acts very much as it does upon the skin, and diluted with water is very useful in *coryza*, and even, by enemata, in *dysentery*; in *croup* or *laryngitis* it may with advantage be applied freely by means of a large camel's-hair brush to the orifice of the larynx, so as to run into the latter. In laxative doses it is asserted to be very effective in *hemorrhoids*. It also forms an excellent basis for mouth-washes; or a paste may be made with it and borax, or similar substance, for use in ulcerations of the same cavity. The list of diseases in which this remedy is employed might be very much lengthened; but the examples already given are sufficient to indicate the range of its application as an emollient and as a vehicle. There are certain persons upon whose skin and mucous membranes even the purest glycerin seems to act as an irritant. This influence is most intense when the glycerin is nearly or entirely free from water. It is, however, discernible even when the remedy is much diluted, and often inhibits its use. The existence of this idiosyncrasy to glycerin can be determined only by trial.

When administered internally in doses of one or two ounces, glycerin acts as a gentle but very uncertain laxative. It was proposed many years ago as a substitute for cod-liver oil in *cachectic diseases*, but has failed to come into use. It has also been highly commended in *diabetes*,\* but is of no service. It is valuable as a harmless substance which has the power of disguising nauseous medicines. In this way it may be employed with castor oil, in emulsions of turpentine, in solutions of iron, and in various mixtures. It seems as it were, to envelop the medicinal substances and prevent their acting on the palate.

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\* For literature and discussion of point, see *Ziemssen's Encyclopædia*, xvi.

## BENZOSULPHINIDE.

*Saccharin*\* is a substance discovered by Fahlberg in 1879. Chemically it is an imide derived from the toluene of coal-tar. It occurs as a white powder composed of irregular crystals, very slightly soluble in water, readily soluble in glycerin, alcohol, and ether. Its watery solution has a distinctly acid reaction, and it forms salts. Its most remarkable property is its sweet taste, which is said to be three hundred times more intense than is that of sugar, so that if one grain of it be dissolved and neutralized in about ten pints of water its presence can still be recognized. Taken internally, saccharin is rapidly absorbed; it is eliminated unchanged chiefly through the kidneys, Bruylants having recovered about eighty per cent. of it from the urine. It has been found by Bruylants in the milk of a nursing woman, and by Hedley abundantly in the saliva. Its influence upon man and animals is very slight; Mosso and Aducco administered seventy-five grains to a man without sensible effect, and found that frogs will live for months in a solution rendered neutral with soda; also, that six hundred grains given to a dog during ten days caused no change in the daily renal excretion of water, urea, hippuric acid, sulphuric acid, or phosphoric acid, and no alteration of the weight or of the general health. On the other hand, it appears to have a feeble influence upon various fermentations. Its solution has antiseptic properties, and in Plugge's numerous experiments it checked the action of ptyalin, pepsin, trypsin, and other allied ferments. Sawitzki, indeed, alleges that it depresses proteid metabolism. In Bruylants's trials it failed to check artificial gastric digestion, probably on account of the acidity of the solution, but as little as one per cent. is enough distinctly to lessen the activity of pancreatin solutions. The general innocuousness of saccharin is, in accord with our own experience, asserted by Salkowski, by Bruylants, by Dreschfeld, by Levenstein, and by other clinicians. Mixed with sodium bicarbonate, two parts to three, saccharin becomes soluble. Its chief value in practical medicine is as a substitute for sugar in *diabetes*, *obesity*, and other diseases in which sugar is contraindicated, but the observation of James Little, that when freely given it is of great antiseptic value in the treatment of *ammoniacal urine*, from cystic, prostatic, or other diseases producing retention or fermentation, is probably correct. It may be used freely as an article of diet, in the form of a solution in glycerin; for medical purposes it is sometimes administered in compressed pills: dose, five grains (0.3 Gm.).

**KAOLIN.**—*Porcelain Clay.*—*Fuller's Earth* is a white powdery clay, unctuous when moist, a hydrated aluminum silicate. It is largely used in the arts for the purpose of clarifying and decolorizing oils and other fluids. It is a non-irritant, inert substance, which is

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\* The present is probably as good as any other place in this treatise to notice a substance whose use in practical medicine depends upon its lack of medicinal properties.

well fitted for thickening ointment or paste. It enters into the official CATAPLASMA KAOLINI, U. S., *Cataplasm of kaolin*, a thick, paste-like substance containing 57.5 per cent. of kaolin, 4.5 per cent. of boric acid, .05 per cent. of thymol, .2 per cent. of methyl-salicylate and 0.5 per cent. of oil of peppermint, held together with 37.5 per cent. of glycerin. A vast amount of nonsensical rubbish has been written and believed of the virtues of this paste. It possesses however no virtues that do not belong to the flaxseed poultice and is probably even less efficient.

POULTICES.—Poultices are moist, soft, scarcely adhesive, perfectly bland plasters, used to a very great extent to combat superficial inflammation. Poultices are much more powerful agents than are the true fatty emollients, and are correspondingly more capable of being abused: the results of such abuse will be spoken of directly. A poultice may, of course, be stimulating and irritant if made of such a substance as mustard; but the ordinary emollient or true poultice is prepared out of some bland material which is totally free from action upon the skin, and depends for its remedial power solely upon the warmth and the water which it contains. Water, when pure and of a temperature approximating that of the body, is a sedative, checking all action, possibly by a direct influence, but probably by the merely mechanical acts of dilution of the pabulum and of separation of the germinal granules. It is also a relaxant, rendering all tissues soaked in it soft and yielding.

Poultices are sometimes applied in the early stages of phlegmonous and other superficial inflammations, for the purpose of checking the morbid action. Their influence is in such case simply one of sedation, and they are certainly not so efficient as the cold-water dressing. They are, however, especially useful in the advanced stages of inflammation, when suppuration has already commenced or is about to set in. Clinical experience has demonstrated that they then favor the formation of pus. Further, the poultice in the latter stages of a superficial phlegmon not only hastens the formation of pus in the inflammatory focus, but lessens irritation in the outlying parts by its sedative action, and so softens the tissues as to aid in the passage outward and the discharge of the inflammatory products. When poulticing is too long persisted in, the part becomes pale or white, swollen, relaxed, and has a sodden look; the granulations of the ulcer or abscess are large, pale, and very flabby, and all the vital actions are below the normal point. It is possible that even death of a part might be brought about by continuous poulticing. Be this as it may, after the discharge of pus, whenever the parts put on the aspect just spoken of, the poultice should be removed and stimulating applications substituted.

Any material which is in itself physiologically inert, and will long retain water, may be used as the basis of the poultice. *Flaxseed meal* is cheap, and is probably the most used of any substance.



*Ground slippery elm* makes a very elegant mucilaginous poultice. Ordinary *Indian-meal mush* is often used. The *bread and milk poultice* is non-irritating, but is prone to undergo putrefaction. The poultice is rarely aseptic, and is often a carrier of germs. This in a measure may be prevented by boiling the poultice just before putting it on; but even with this precaution, when applied to an infected wound, poultices, by retaining and stimulating the growth of germs, often increase the inflammation. For this reason other methods of applying warmth and water have largely replaced the old-fashioned poultice. Spongiopiline, or absorbent cotton, or similar material, which is readily rendered aseptic, and is incapable of undergoing fermentation, when saturated with heat and water affords an application which is practically a poultice, and which may be rendered germicidal by the addition of minute quantities of corrosive sublimate or similar substances, as called for by the exigencies of the case.

Poultices are frequently used in the treatment of deep-seated inflammations. Under these circumstances, according to the dictates of experience, they should be applied very hot, and be frequently renewed; very often, too, a small amount of mustard or of some similar stimulating material is added to them with advantage. As a result, these poultices act as gentle but deep-reaching counter-irritants, which in all likelihood affect not merely the blood-vessels of the skin, but also those of the subdermal tissue. When it is borne in mind that in all these cases the poultice is applied to a very large surface, it will readily be perceived that this counter-irritation is a powerful one. Thus, in *pleurisy* or in *pneumonia* the whole anterior or posterior surface of the chest is covered, or perhaps the whole chest is enveloped, by the jacket-poultice. In *peritonitis* the poultice should be as large as the abdomen of the patient. In either of these cases the amount of blood drawn to the surface must be considerable. It is probable that the water of the poultice in some cases actually soaks through and exerts its direct sedative influence upon the affected tissue. The value of poultices in lung diseases is much greater in children, whose chest-walls are very thin, than in adults; and it is not illogical to believe that the difference may be dependent upon the inequality of the chest-walls.

The *jacket-poultice* should be made of thin flannel formed into a sort of double bag, so cut and shaped as to fit the individual, and secured in front with safety-pins and over the shoulders with tapes, or it may be fastened directly to an undershirt, a piece of oiled silk always being placed directly outside of the jacket. The jacket should be divided into two parts by a horizontal line of stitching, and be filled from one end. In order to prevent sagging of the contents, it is well, after filling, to take a stitch here and there, in the manner of quilting. The effect of a jacket-poultice may be imperfectly attained by covering the patient with wool batting and oiled silk outside of this,—in fever patients the moisture from the surface and the heat of the body serving to form a kind of fomentation.

The value of the jacket-poultice in disease is, however, greatly lessened by the fact that it enormously increases the heat-retention

of the body, and has, therefore, in many cases a very serious influence in heightening a fever temperature whose reduction is urgently indicated. Whenever, in a *pneumonia*, the temperature is high, the application of cold water by means of compresses, or absorbent cotton, is preferable to the use of the jacket-poultice. In cases of *peritonitis* the sensations of the patient are often a practical guide to the choice of the dressing. If the pain is aggravated by external warmth, the cold-water dressing is preferable; while, if the cold-water dressing is steadily obnoxious to the patient, the best results may usually be achieved by the use of hot water.

**COLLODION.**—This is a solution in alcohol and ether of pyroxylin or soluble gun-cotton, which consists chiefly of the tri- and tetra-nitro-cellulose; upon evaporation collodion leaves on the skin an adherent protecting film.

Physiologically, gun-cotton is inert. Collodion is a colorless, slightly opalescent liquid, of a syrupy consistence, and smelling strongly of ether. By long standing it deposits a layer of fibrous matter, and becomes more transparent. This layer should be re-incorporated, by agitation, before the collodion is used. When it is applied to the skin, and the menstrua are allowed to evaporate, collodion forms an impervious, colorless, transparent, flexible, and strongly contractile film, which adheres very closely, and cannot readily be removed. The contractility of the film may in a great measure be destroyed by the addition to the collodion of certain substances, as in flexible collodion, which contains five per cent. of Canada turpentine and three per cent. of castor oil, and on evaporation leaves a film which does not contract.

As a substitute for collodion the non-official solution of gutta-percha in chloroform (*Liquor Gutta-Perchæ*) is sometimes employed.

#### Official Preparations :

Collodium.....	External use.
Collodium Flexile.....	External use.
Collodium Cantharidatum (Cantharides 60 per cent.).....	External use.
Collodium Stypticum (Tannic Acid 20 per cent.).....	External use.

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## DIVISION II.—EXTRANEOUS REMEDIES.

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THESE are drugs which are employed not to act directly upon the human system or upon any of its tissues, but upon some extraneous material or entity, either in the cavities of the body or upon its exterior. Thus, an antacid neutralizes acid in the stomach, or an anthelmintic kills the tapeworm in the intestines, or a disinfectant destroys poisonous emanations in the exterior world and thereby wards off disease.

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### FAMILY I.—ANTACIDS.

ANTACIDS are, strictly speaking, substances which are capable of neutralizing acid. The class, as here defined, contains those remedies which in medicine are used for the purpose of neutralizing an excess of acidity in the *primæ viæ*. They are almost solely employed in forms of *dyspepsia*. Without doubt, *cardialgia*, *gastric uneasiness*, *heartburn*, and the rising of sour water in the mouth are often the result of too much acid in the stomach, perhaps secreted by a perverted glandular action, but more probably in the great majority of cases formed by fermentative changes in the partially digested food. As excessive acidity of the stomach causes gastric uneasiness and derangement, so will a similar condition of the intestinal canal cause pain and spasm and functional disturbance in the bowels. This is seen most frequently in infants, and is very often associated with a diarrhoea in which the passages have a green color, similar to that of spinach, and hence are sometimes spoken of as “spinach-stools.” In *diarrhœa* of this character, as well as in *colic*, antacids are often of service by neutralizing the acid in the intestinal canal.

Clinical experience has demonstrated that dyspepsia is often permanently relieved by the use of alkalies when they are given steadily day after day, for a long time. According to Thomas K. Chambers, this is dependent upon an effect pointed out by Claude Bernard,—the augmentation of the acid gastric juice, and so of the normal peptic powers of the stomach. The same authority further says, “The test of benefit being derived from an alkali is the dose not requiring to be increased as the patient goes on taking it, but, on the contrary, being diminished gradually, while relief from the recurrence of heartburn continues still to be experienced.”



*Sick headache* is sometimes dependent upon gastric irritation produced by an excess of acid in the stomach. This true sick headache is generally to be distinguished from migraine by the early occurrence of the stomach symptoms, either as heartburn, nausea, vomiting, or simple gastric distress, and by the fact that the pain comes on with an attack of blindness or of dizziness, and is not limited to any one spot, as the supra-orbital or other neuralgic foci, but is felt all across the brows. In this form of cephalalgia antacids often afford prompt relief.

Various substances which have already been discussed in this work are excellent antacids, most of them uniting this to other medicinal properties. Thus, when a stimulating antacid is desired, as is very often the case in sick headache, half a drachm of the *aromatic spirit of ammonia* may be taken, well diluted with water. *Potassium* and its carbonates have already been dwelt upon with sufficient detail. They may be used as antacids; but, as they exert other powerful influences upon the system, they are, we think, not so generally useful as the soda preparations.

### SODIUM.

The alkaline salts of sodium include the hydroxide, carbonate and bicarbonate.

*Sodium hydroxide* is usually found in the form of white or nearly white sticks or pencils which deliquesce and subsequently absorb carbonic acid.

*Sodium carbonate* is found commercially united with various proportions of water of crystallization. The Pharmacopœia recognizes only the mono-hydrated sodium carbonate; this is a white crystalline granular powder without odor but with a strongly alkaline taste. It is soluble in 2.9 parts of water and insoluble in alcohol.

*Sodium bicarbonate* is a white odorless powder with a mildly alkaline taste soluble in 12 parts of water at 59° F. At higher temperatures it gradually loses carbonic acid and is changed into a carbonate. It gives a slightly alkaline reaction with litmus.

#### Official Preparations:

Sodii Hydroxidum [Caustic Soda].	.....	Not used internally.
Liquor Sodii Hydroxidi (5 per cent.).	.....	15 minims (1 C.c.).
Sodii Carbonas Monohydras [Washing Soda].	5 to 10 grains	(0.3-0.6 Gm.).
Sodii Bicarbonas [Baking Soda].	.....	10 to 20 grains (0.6-1.2 Gm.).

Soda \* being the normal alkali of the blood, even very large doses of it have very little influence upon man or mammalia, but it is probable that it acts much more powerfully on cold-blooded animals.

Grandeau found that one hundred and seven grains of sodium carbonate injected into the vein of a dog produced only very slight symptoms, and that thirty-

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\* As Rabuteau found that in dogs with gastric fistula both the quantity and the acidity of the gastric juice are decidedly increased by the use of salt meat, it would appear probable that the local action of common salt upon the stomach is that of a stimulant.

five grains of the nitrate similarly administered to a rabbit caused only some convulsive movements. According to Guttman, however, the sodium salts thrown directly into the blood in very large amounts will slowly cause death, the agony being very prolonged, and, when the chloride is used, convulsions being developed. Both Podocæpow and Guttman assert that even the largest doses do not sensibly affect the heart or the temperature; and the latter observer further declares that they are without influence upon the nerve-centres, the peripheral nerves, or the muscles. But if this be the case, it is difficult to perceive how they can cause death; and the earlier experiments of Podocæpow indicate that they do exert a very feeble action upon the peripheral nerves or the muscles. Curci also finds that the sodium salts increase the blood-pressure after the destruction of the oblongata, and believes that they influence the peripheral vaso-motor nerves. H. G. Beyer, as the result of experiments made upon terrapins, comes to the conclusion that sodium salts excite first the ganglia of the vaso-dilator nerves and afterwards those of the vaso-constrictor nerves.

Although Mayet affirms that sodium chloride increases the elasticity of the red blood-corpuscles, the immediate influence of the sodium salts upon the blood\* is probably very slight, since, according to Podocæpow, one part dissolved in twelve parts of blood does not affect either the physical characters of the red corpuscles or the intensity of the ozone reaction.

Podocæpow and Schönlein both affirm that they cause in the frog spinal convulsions, but in Ringer and H. Sainsbury's experiments the influence of the sodium salts upon the frog was found to be so slight that they could hardly be made to kill. It seems established, however, that they will produce cataracts in the frog.† Most observers state that the sodium salts are capable of arresting the frog's heart in diastole, either when it is in position or after it is removed from the body; and Laffout states that there is a primary period of cardiac stimulation, which is in accordance with the observation of T. W. Mills upon fishes. There is, however, much difference of statement by different observers in regard to the action of these salts upon the frog's heart.‡

*Nutrition.*—A certain amount of soda is a necessary food for the higher animals, yet it is very doubtful whether an habitual excess has decided effect upon the nutrition, the general drift of the present evidence being to show that when in excess the sodium salts neither increase nor yet decrease the elimination of urea or other products of tissue-waste.

In the experiments of Münch the continuous exhibition of large doses of common salt to man apparently produced at first a slight diminution of excretion and a corresponding gain of the body in weight; but after a time the excretion increased and the weight of the body decreased. The variations in excretion affected chiefly the urine, but sometimes the perspiration and feces were also influenced. The urine was rendered alkaline, but its solid ingredients were scarcely at all affected. The conclusion of Damourette and Hyades, that salt increases the elimination of urea and uric acid, is not warranted by their own experiments; and in the researches of I. Mayer, of A. Ott, of C. Clar, and of L. Klemptner, neither the sodium citrate, acetate, phosphate, or sulphate increased nitrogenous elimination, while in those of Dalebe and Carberet the alkaline sodium salts reduced the output of urea.

\* Kowalewsky records in the *Centralbl. f. Med. Wissen.*, 1887, the results of an elaborate study of the effects of adding, either in solid form or in concentrated solution, salts of potassium, sodium, lithium, and ammonium to the blood. As it is not possible at present to connect this influence with the effects of therapeutic doses of the drug inside of the body, we content ourselves with referring to the paper.

† For a discussion of this, and literature on the subject, see Limbourg (*Arch. f. Exper. Path. u. Pharm.*, 1888, xxiv.). For a series of papers on the antagonistic actions of sodium, potassium, and calcium salts on the frog, by Sydney Ringer, see *Journal of Physiology*, 1890, 1894, 1895.

‡ See Podocæpow (*Virchow's Archiv*, xxxiii. 507), Schönlein (*Arch. f. d. Ges. Physiol.*, xviii. 26), Laffout (*Compt.-Rend. Soc. Biol.*, 1880, 282), Ringer and Sainsbury (*Lancet*, 1882, ii. 736), Ringer (*Brit. Med. Journ.*, 1884), Limbourg (*Arch. f. Exper. Path. u. Pharm.*, 1888, xxiv.).

**Therapeutics.**—The fact that soda, in moderate amount, has no depressing action, and indeed very little, if any, influence upon the general system, renders it preferable to potassium in cases of acidity of the *primæ viæ*. It is *par excellence* the alkali for *acid dyspepsia*. On the other hand, the circumstance clearly established by Roberts, that it is less powerful as a solvent of uric acid than is its sister alkali, together with the property, believed to belong in a much greater degree to potassium, of preventing the formation of uric acid, makes sodium of very inferior value in *uric acid gravel* or *uric acid diathesis*. When in any case it is desirable simply to render the urine alkaline, and at the same time to avoid depressing the system generally, soda would, on theoretical grounds at least, seem preferable.

It appears to be well proved, clinically, that the alkaline sodium salts given one to two hours before meals in full doses are of decided value in the treatment of *chronic hepatic torpor*, of *catarrhal jaundice*, and especially of *gall-stones* or other affections associated with excessive viscosity of the biliary secretions.

As the result, however, of an elaborate series of experiments made upon dogs with biliary fistula, J. Glass concludes that the alkalies given by the mouth do not increase the alkalescence or amount of the bile. The caution necessary in applying such experiments to human medicine has been spoken of in an earlier chapter. Moreover, it was apparently proved by the experiments of S. W. Lewaschen that the sodium carbonate, sulphate, or phosphate, given to dogs with biliary fistula, increases very markedly the liquidity of the bile by diminishing the percentage of solids. The sodium salicylate acted similarly to, but much more powerfully than, the other salts. E. Dufourt, experimenting with the sodium bicarbonate upon dogs, found that there was a very constant and pronounced increase both of the glycogen and of the sugar of the liver.

A possible therapeutic use of sodium carbonate is suggested by the experiments of W. H. Howell, who found that in the lower animals intravenous or rectal injections of solutions of sodium carbonate increase markedly in animals suffering from *shock* the amplitude of the heart-beat, and cause a rise of arterial pressure. Dalebe and Carteret affirm that in *diabetes*, especially of the azoturic form, sodium carbonate is a very valuable remedy.

Although so harmless, the sodium salts when in great excess are decidedly irritant, and it has been shown by Stokvis and Levi that it is possible with the sodium chloride to produce albuminuria, tube-casts, and organic renal changes.

As an antacid the bicarbonate should usually be selected, as being the least irritant.

### MAGNESIA.

The *heavy* and the *light* magnesia differ only in their physical characters, the particles being differently aggregated. Magnesium carbonate is manufactured by precipitating a solution of magnesium sulphate by one of sodium carbonate. If the two solutions be concentrated, the dense or heavy carbonate will fall; on the other hand,



if the solutions be dilute, the precipitate will be a light carbonate. Heavy magnesia is obtained by calcining a heavy carbonate; light magnesia, by using a light carbonate. All of these substances are of a milk-white color, and occur in powder; the carbonates sometimes in very light cubical blocks. They are all practically insoluble in water, freely soluble in dilute acid, and in the presence of acids they all act as alkalies.

#### Official Preparations :

Magnesii Oxidum [Calcined Magnesia].....	1 to 4 drachms (4-15 Gm.).
Magnesii Oxidum Ponderosum.....	1 to 4 drachms (4-15 Gm.).
Magnesii Carbonas.....	1 to 4 drachms (4-15 Gm.).

**Therapeutics.**—Magnesia and its carbonate are antacid and laxative. For their purgative powers they are probably dependent upon the presence of acids in the primæ viæ, and hence their effects vary. When taken repeatedly they are said at times to accumulate in the intestines, and should not be used as an habitual laxative. They are often given along with Epsom salt or senna, on account of their antacid properties. Their chief use is in acute *acid dyspepsia*, in *sick headache*, in *diarrhæa* with excessive acidity in children, in *gout*, in *rheumatism*, and in various *cutaneous affections*,—wherever, in a word, a laxative antacid is indicated.

### CALCIUM.

Of the numerous salts of calcium there are considered here only those in which the action of the basic ion predominates. These are the oxide, the carbonate, and the chloride.

*Calcium oxide*, or lime, is made by calcining the carbonate, and occurs as white or grayish white masses which when exposed to the air absorb carbonic acid and crumble to a white powder. When moistened with about one-half its weight of water there is formed with the evolution of much heat, a white powder, calcium hydroxide or slaked lime. Lime is soluble in 760 parts of water at 77° F. but becomes less soluble as the temperature of the water is raised, so that boiling water will dissolve but one part in 1600.

*Calcium carbonate* is a very widespread natural salt, being the basis of marble, chalk, and Iceland spar. The U. S. Pharmacopœia recognizes two forms of calcium carbonate, namely, prepared chalk and the precipitated calcium carbonate. Each of these occurs as a white powder practically insoluble in water, although small quantities may be dissolved in solutions of carbonic acid.

*Calcium chloride* is seen in the form of white semi-translucent fragments, odorless but with a sharp saline taste. It is soluble in 1.3 parts of water and 8 parts of alcohol, and is extremely deliquescent.

*Calcium sulphate*, or plaster of Paris, is a fine white powder with a faint earthy odor, which is prepared by heating gypsum until most of the water is expelled. It is used in medicine for purely mechanical purposes. It absorbs water and in a few minutes solidifies.

**Official Preparations :**

Calx [Calcium Oxide: Lime].....	Not used internally.
Liquor Calcis [Lime Water] (0.14 per cent.)..	1 to 4 fluidrachms (4-15 C.c.).
Syrupus Calcis (6.5 per cent.).....	10 to 20 minims (0.6-1.2 C.c.).
Linimentum Calcis [Carron Oil].....	External use.
Calcii Carbonas Præcipitatus.....	15 to 60 grains (1-4 Gm.).
Creta Præparata [Prepared Chalk].....	15 to 60 grains (1-4 Gm.).
Pulvis Cretæ Compositus (30 per cent.).....	$\frac{1}{2}$ to 1 drachm (2-4 Gm.).
Mistura Cretæ (6 per cent.).....	$\frac{1}{2}$ to 1 fluidounce (15-30 C.c.).
Calcii Chloridum.....	10 to 30 grains (0.6-2 Gm.).
Calcii Sulphas Exsiccatus [Plaster of Paris]..	Not used internally.

*Local Action.*—Unslaked lime is an active escharotic; slaked lime is an irritant, or, when in concentrated form, a feeble escharotic.

*Absorption and Elimination.*—Lime is never used in substance in medicine, but in the form of a aqueous solution. When in such dilute form it acts as a detergent and sedative, especially to mucous membranes. Its official insoluble preparations are free from irritant properties and are mild astringents. Neither the soluble nor insoluble preparations of lime are absorbed to any large extent, the lime escaping, if given in considerable dose, in great part with the feces in the form of some insoluble salt. Minute quantities of it probably circulate in the blood in combination with proteids.

When a soluble salt of calcium is given intravenously, an insoluble form of lime is probably rapidly deposited in the tissue. Excretion of lime chiefly takes place through the urine, or perhaps more largely through the large intestine.

**Physiological Action.**—Probably owing to the difficulty of their absorption, even the soluble preparations of lime have not been found in practical medicine to have any general effect upon the body. Carl Franke, indeed, states that the intravenous injection of large amounts of soluble lime salts has no effect upon rabbits.

The soluble salts of lime are evidently not without physiological activity, and have close relation with the general bodily well-being. W. H. Howell and E. Cooke have proved that the inorganic salts of the blood, milk, gastric juice, etc., are able to keep the isolated frog's heart beating with force and regularity for many hours without other food, and, according to the experiments of Ringer, among these salts those of lime are especially important. Further, it seems to be demonstrated that small doses of soluble calcium salts increase the energy of the heart's action, as the experiments of Ringer have been confirmed by Mickwitz and also by Binet. Langendorff and Hueck believe that their own and previous experiments justify the conclusion that the presence of calcium in the nourishing liquid is absolutely essential for the continuance of the cardiac action, not only in cold but also in warm-blooded animals. Binet states that though the cardiac arrest usually takes place in systole in calcium-salt poisoning, yet if the salt have come directly in contact with the heart in concentrated form there is paralytic arrest (diastolic). Further, according to Ringer and to H. G. Beyer, the voluntary and involuntary muscles of the frog are stimulated by small amounts of calcium; and, according to Franke, they are paralyzed by large amounts of the drug. Stefani states that calcium chloride when applied locally in minute amount increases the functional activity of the motor nerve-trunks, but when in large amount produces rapid paralysis; while Binet has demonstrated that the toxic dose of the calcium salt directly paralyzes the cerebral cortex and the motor centres of the spinal cord.

It is certain that the calcium salts are essential to all the higher tissues. It is probable that under ordinary circumstances a sufficiency of these salts is furnished to the system by the food, and that no gain is to be achieved by their further administration. This is, however, only a probability, not a definitely demonstrated fact; it may be that the soluble haloid salts have more practical value than is at present believed.

**Therapeutics.**—As antacids the salts of lime are used largely in the treatment of *diarrhœas*, not only because none of the calcium salts are laxative but also because they seem to exercise a mildly astringent influence.\* For this purpose one of the preparations of the carbonate is generally preferred, although the syrup of lime is occasionally employed.

In *vomiting*, from almost any cause except acute gastritis, equal parts of lime-water and milk afford an elegant, simple, and much-used remedy. If the vomiting be severe, all other food should be inhibited, and one or two tablespoonfuls of the mixture given every half-hour,—the quantity, as well as the proportion of milk, being increased as the stomach is able to bear it. As lime-water when put in milk prevents the formation of dense coagula, it is often added with advantage to that fluid when used as food for infants, or for adults with weak digestion.

Externally, lime-water has been used as a wash in various skin diseases, especially in *tinea capitis*: it is also applied to *ulcers*, and is said to have a very marked influence in lessening the amount of discharge. When mixed with an equal bulk of linseed or olive oil lime-water forms a thick, soapy liquid (*Carron Oil*, so called from the name of the iron-works at which its reputation was first made), which is much used in recent *burns*.

Lime-water has the power of dissolving mucus and also false membrane, and has therefore been introduced as a local remedy in *pseudo-membranous croup* and in *diphtheria*. It is sometimes used by causing the patient to inhale the vapors of slaking lime, but a better method is to pulverize lime-water by means of an atomizer and direct the spray upon the back of the fauces while the patient is respiring deeply. The application should be made every two or three hours.

Externally, prepared chalk and precipitated calcium carbonate are used as desiccants and protective applications to *ulcers* and *chronic burns*, also in *excessive sweating* of the feet, and in *intertrigo* and other *affections of the skin*.

CALCIUM CHLORIDE is locally a violent irritant, but it is strongly recommended by Sée in the treatment of *gastric catarrh* and fermentative *dyspepsia*. The results of experimental studies as to the action

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\* J. Bruce MacCallum (*University of California Publications*, Vol.i,—confirmed by Ott) has found that calcium chloride very markedly inhibits peristalsis in the rabbit, and suggests its use in *nervous diarrhœa*.



of calcium chloride upon the heart suggest the probability that when hypodermoclysis is indicated in conditions involving also cardiac failure, the addition of chloride of calcium to the normal saline solution might be of great service.

Calcium chloride is also largely used in the treatment of internal hemorrhage with the idea that it increases the coagulability of the blood. While there is some evidence that, when injected into the vessels directly, it has such an action, it is probably not absorbed from the intestinal tract in sufficient quantity to exercise any marked influence.

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## FAMILY II.—ANTHELMINTICS.

THESE are medicines which kill or cause the expulsion of intestinal worms. They are sometimes divided into *vermicides*, those which kill, and *vermifuges*, those which expel; but there is little or no practical use in the division. It is of much greater importance to establish the relations between these drugs and the different species of entozoa, since clinical experience has demonstrated that an anthelmintic very efficient against one form of intestinal worm may be not injurious to another species. Therapeutically considered, the entozoa may be divided into the *Tapeworms* (*Tæniæ*), the *Round-worms* (*Lumbrici*), and the *Seat-worms* (*Ascarides*). The last of these differ from the others in that they are to be attacked solely by enemata.

It is obvious that the value of an anthelmintic depends not only upon its power of poisoning the articulate, but also upon its harmlessness as regards the patient. Thus, it is the eminent combination of these qualities that renders the infusion of quassia so valuable in cases of seat-worms, while phenol, though very efficient, should never be used against the same parasite, since it has greatly imperilled, if it has not destroyed, the life of the patient when so employed.

There are certain general rules which govern the administration of anthelmintics, and which should not be lost sight of. They may be summed up as follows:

Let the alimentary canal be as empty as possible, so that the drug may act with the greatest force upon the enemy. For this reason, anthelmintics are best administered early in the morning; and in obstinate cases the patient should be required to fast until dinner-time. If the drug be not itself a purgative, from four to eight hours after its administration a brisk cathartic should be given; or a purgative dose of calomel may be combined with it, as the bilious purging induced by the latter drug seems to be especially obnoxious to the entozoa.

### SANTONICA.

*Levant Wormseed* consists of the unexpanded flower-heads of *Artemisia pauciflora*, a composite of Northern Middle Europe and Asia. It consists of pale, greenish-brown, smooth heads of four or five tubular flowers of a very strong aromatic odor when rubbed, and a bitter, disagreeable taste. It contains volatile oil, resinous matter, and a crystalline principle, *santonin*, the anhydride of *santoninic acid*, which occurs in colorless, pearly, four-sided, ortho-rhombic, very insoluble tables. It has a neutral reaction, but unites with alkalies to form salts, and hence is freely soluble in alkaline solutions.

**Official Preparations :**

Santoninum.....	2 to 4 grains (0.13–0.26 Gm.).
Trochisci Santonini (each $\frac{1}{2}$ grain).....	2 to 6 troches.

**Physiological Action.**—*Absorption and Elimination.*—Santonin is only feebly irritant. It is absorbed readily, probably as a sodium santoninate, and by its elimination produces a very pronounced reddish discoloration of the urine, which is characteristic of the poisoning.

According to the researches of Jaffé, santonin is eliminated as a new substance—*santogenin*, and also as a derivative of santogenin— *$\beta$ -oxysantonin*.

The color of the urine is a very marked yellow, which has at first an orange tint, but after very large doses becomes saffron-like, or sometimes even a purplish red, which has given origin to the idea that blood was present in it. According to Manns, the addition of an alkali to the yellow urine causes it to become red.

The exact form in which santonin is thrown off is not established, but probably it undergoes oxidation in the system. Kletzinsky asserts that the drug receives in the system six atoms of oxygen.\*

Santonin must have a powerful action upon the nervous system, but we have no detailed knowledge as to its general physiological action. Santonin often increases the flow of urine, and, according to Farquharson, it also increases slightly the elimination of urea.

**Therapeutics.**—Santonin was introduced into therapeutic use in 1830 almost simultaneously by Alms and by Kahler, and is one of the most reliable remedies that we have in the treatment of the lumbricoid or round-worm. Von Schröder believes that he has proved by direct experiment that santonin is feebly toxic to the round-worm; but in this he is in opposition to the general clinical experience and the almost universal belief of helminthologists that santonin acts directly upon the intestinal parasite. It certainly is a very efficient remedy, but it should either be combined with or followed in about two or three hours by a brisk cathartic. The combination of calomel and santonin has been much commended.

As long ago as 1862 Guépin and Martin recommended santonin in *amaurosis*, asserting it to be especially useful in those cases in which there had been choroiditis and iritis. These statements have been confirmed by D. Dyce Brown, as well as by Ogston. G. Frank Lydston affirms that santonin is a valuable remedy in *epilepsy*. D. H. Bergey asserts that santonin has especial relations with the uterus, and, if given in full dose at the time of the *molimen*, is an efficient remedy in *acute suppression of the menses*.

**Toxicology.**—The first and most characteristic symptom produced by large doses of santonin,—*xanthopsia*, or yellow vision, is probably due to a direct action of the poison upon the retina.

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\* Chrysophanic acid produces a discoloration of the urine similar to that caused by santonin. According to Hoppe-Seyler, the cause of the coloration can readily be distinguished by adding sodium hydroxide to the urine, and then shaking up with amyl alcohol, when, if the coloration proceeds from santonin, the urine is decolorized, while, if it be due to chrysophanic acid, the alcohol takes up only traces of the coloring matter.



Xanthopsia was first noticed by Calloud. Usually it consists of a very deep yellow tint imparted to the landscape and to every object looked at,—an effect perhaps most comparable to that of looking through yellow glass; sometimes this yellow is replaced by green; and Heydloff states that he has seen patients in whom the tint was red, and others in whom it was blue. As was first pointed out by Knies, the period of yellow vision is usually preceded by one of violet vision, and during the stage of yellow vision there is a lessening or complete destruction of the sensibility towards the violet end of the spectrum. Two theories have been advanced as to the cause of the yellow vision; first, that it is simply due to staining of the humors of the eye, but Rose was unable to find any dyestuff in any portion of the body except in the medulla of the kidney; and Filehne, in a very large series of studies upon human beings and lower animals was unable to find any staining either of the humors or of the retina itself. Moreover, the theory of staining does not satisfactorily account for the violet vision which precedes the yellow, nor for the later failure of the power of recognizing violet. The second theory, that the disturbance of vision is due to the action of the drug upon the retinal elements themselves, would seem to be strengthened by the statement of Filehne that changes in the visual purple can be demonstrated in animals fatally poisoned with santonin. The accuracy of this statement is, however, denied by Knies, who affirms that santonin has no influence upon the visual purple or the function of the rods of the retina, so that the matter would seem to be still *sub judice*.

In poisoning by santonin great pallor of surface, with a blue color around the eyes or involving the whole countenance, has been generally an early symptom; vomiting has not rarely been present, and sometimes has been accompanied by colicky pains. Besides these manifestations, giddiness, mental apathy or stupor, great coldness of the surface, profuse sweating, trembling, mydriasis, and finally loss of consciousness, with convulsions, often violent and accompanied by opisthotonos and emprostotonos, and failure of respiration, are the usual phenomena of santonin-poisoning. The circulation seems to be very little affected.\*

According to Fröhner, moderate doses of santonin produce in domestic animals polyuria, sometimes strangury, and very commonly so pronounced sexual excitement as to suggest that the drug may have value as an aphrodisiac. The toxic dose causes in dogs and other domestic animals accelerated breathing, slowing of the pulse, universal trembling, cramps, free salivation, unconsciousness, convulsions, dilated pupils, and death.† After death the lesions are not absolutely constant, but hyperemia of the nerve-centres and congestion of the lungs and heart are nearly always present.

The smallest dose causing fatal poisoning, which we have seen, is that reported by Grimm. In this case, a rather feeble child five years old took two one-grain doses of santonin, and was seized with convulsive tremblings, which increased in severity until they became severe convulsions, accompanied by unconsciousness, trismus, pallor of the face, cold sweats, dilated pupils, and rapid pulse and respiration. Thirteen or fourteen hours after the ingestion of the poison, while the patient lay on her back, quiet, unconscious, with moderately

\* Case, *Arch. für Exper. Path. und Pharm.*, vi. 302.

† See experiments of Manns (*Das Santonin*, Marburg, 1851), of Rose (*Virchow's Archiv*, 1850, xvi.), of T. Krauss (*Inaug. Diss.* Tübingen, 1869), and of Fröhner (*Monatshefte f. Thierheilk.*, 1893, iv.).

dilated pupils and a slow, feeble pulse, death occurred suddenly. In several other instances doses of from four to six grains have proven fatal to children.\*

It is a curious fact that some of the text-books advise the use of santonin in doses larger than those which have produced serious or even fatal poisoning. Very alarming symptoms have been occasioned in a child three and a half years old, by one and one-half grains. The reason large doses have been so often given with impunity is the great insolubility of the crystals of the drug.

The *treatment* of poisoning by santonin, after evacuation of the stomach and bowels, must at present be entirely tentative. One case appears to have been saved by artificial respiration; but Binz has found amyl nitrite, morphine, and artificial respiration alike useless in animals; chloral given before the poison appeared to be of service.

**Administration.**—Santonin is best administered in *troches*, so that the slow solution of the santonin in the intestine shall produce the greatest possible effect upon the worm with the least absorption of the remedy. The dose for a child two years old is one-quarter to one-half a grain (0.016–0.03 Gm.). For young infants, santonin is hardly a safe remedy in any efficient dose. When a dose of any size is given, it should not be repeated in less than eight hours, and the last dose should be accompanied by a purgative amount of calomel.

The soluble *sodium santoninate* is much more dangerous and less efficient than santonin: the object is to get as much of the remedy as possible in contact with the worm, and, as in order to do this a slow, not a rapid, absorption is necessary, the insolubility of santonin is an advantage.

### SPIGELIA.

The rhizome and roots of *Spigelia marilandica*, or Pinkroot, an herbaceous perennial, growing in the Southern and Southwestern United States. It consists of a knotty head, with numerous fine, crooked, branching rootlets. The odor is faint and peculiar; the taste sweetish and slightly bitter. W. L. Dudley separated from it an alkaloid, *spigeline*, which, according to Boorsma, is actively poisonous.

**Physiological Action.**—Full therapeutic doses of spigelia produce in man no symptoms, but, according to Hodge Thompson (quoted by Eberle), Eberle, and Spalsberg, an overdose causes acceleration of the pulse, dilatation of the pupils, heat and dryness of the skin, flushing and a swollen appearance of the face, with, in Eberle's cases, talkative delirium. Two fatal cases † of poisoning by it are said to have been recorded. According to H. A. Hare, toxic doses slow the pulse and depress the heart, the respiratory centre, and the motor spinal cord.

\* References for these cases: *P. J. Tr.*, viii. 996; ix. 696; *B. G. T.*, lxxiv. 362; *S. Jb.*, cxi. 128. See also W. J. Kilner, *St. Thomas Hosp. Rep.*, and C. Bevil, *T. G.*, iii. 428; Berg, *Wurtemberg. Med. Correspondenzbl.*, 1862.

† These cases appear to have been indefinitely copied, and are of doubtful authenticity.

In Hare's experiments toxic doses of spigelia caused in the dog hurried respiratory movements, retching, wide dilatation of the pupil, internal strabismus, marked exophthalmia, muscular weakness and loss of coördination, and at last sleep, passing into coma and death from failure of respiration; in the frog exophthalmia, excessive muscular weakness, loss of reflex activity, and slowing of the heart, with at first increase of power of the systolic contractions but afterwards arrest in a condition of semi-diastole.

**Therapeutics.**—Spigelia is a most efficient remedy in cases of the round-worm, and is, when given within the bounds of moderation, entirely safe. It appears to narcotize the worm, and requires the use of a brisk cathartic. The only preparation official is the fluidextract (FLUIDEXTRACTUM SPIGELLÆ), the dose of which for an adult is 2 fluidrachms (8 C.c.). It is generally combined with senna.

### OIL OF CHENOPodium.

The *Chenopodium anthelminticum*, or Jerusalem Oak, is a rank, odorous plant, growing about waste places in the suburbs of towns in the United States. The seeds (sometimes known as American wormseed) are minute, globular, are light brown and about the size of a pin's head, of a nauseous odor and a pungent taste, due to the volatile oil which they contain in large quantity.

The oil of chenopodium, the only derivative of the plant official (OLEUM CHENOPODII), is of a light yellow color, becoming darker and less fluid by age, of a peculiar powerful odor and a hot burning taste.\*

According to Brünning the oil of chenopodium produces, in both frogs and rabbits, paralysis through depression of the spinal cord; and in the mammals, paralysis and respiratory failure. Added to blood outside the body it causes methemoglobin. Brünning also finds that in proportions of one part to two hundred it has a distinct antiseptic action; while 1 to 5000 narcotizes but does not kill the *Ascarus mystax* (round-worm of dogs). It has been used in *hysteria*, but is now employed only as an anthelmintic against the *lumbricus*, and more rarely the *tapeworm*. It is very efficient, and ten minims (0.6 C.c.) of it, on sugar, may be given to a child three years old, before breakfast, dinner, and supper, for two days, followed by a brisk purge.

### ASPIDIUM.

*Filix-Mas*, or *Male Fern*, is the rhizome of *Dryopteris Filix-mas*, or male fern of Europe. Under the name of *Aspidium* † the present U. S. Pharmacopœia recognizes both it and the rhizome of the indige-

\* In the *Maryland Med. Journ.* iv. 20, T. R. Brown reports a case in which death was attributed to the taking of an ounce or more of wormseed oil in divided doses. The patient was found in bed unconscious, with vomited matters over his surroundings, after some hours became sensible, relapsed an hour or two later into heavy sleep, was again roused, and while playing cards became aphasic, deaf to conversation, acutely sensitive to other sounds and finally died of hemiplegic apoplexy. It is improbable that the wormseed was the direct immediate cause of the fatal result.

† It is probable that many species of the genus *Aspidium* are active. Poulsson (*Arch. f. Exper. Path. u. Pharm.*, 1895, xxxv.) separated from the rhizome of *Aspidium spinulosum* two acids closely allied to filicic acid, a yellow and a white *polystichic acid*; and both he and Valter Laurén have found these extracts of the plant to be active tæniacides.



nous *D. marginalis*. The rhizome, when perfect, is from six to twelve inches long, and covered with large, brown, imbricated scales. Its taste is bitter and astringent.

The official oleoresin (*OLEORESINA ASPIDII*) thoroughly represents the crude drug. It is a dark, thick liquid, of a bitter, nauseous, slightly acrid taste.

*Aspidium* contains an amorphous acid, *filicic*,\* which, according to the experiments of E. Poulsson, is a very active substance, causing, in the frog, at first excitement and then paralysis of the central nervous system, and finally paralyzing the heart and exerting a marked influence upon the muscles: producing in warm-blooded animals violent diarrhoea, with a general paralysis due to depression of the spinal centres, and finally cardiac palsy. Kobert, however, as the result of his experiments, believes that the vermifuge principles of male fern do not depend solely or even chiefly upon filicic acid, but upon the ethereal oil.

In overdose it is a violent poison, producing excessive vomiting and purging, with general weakness, tremors, cramps in the extremities, increased reflexes, amaurosis, and finally, in some cases, violent tetanic convulsions, with opisthotonos, stupor deepening into coma, and collapse. Icterus is sometimes apparent. Disturbance of the special senses is a not infrequent symptom in *aspidium*-poisoning. Deafness without loss of vision has been noted (case of Grant). More commonly amblyopia or complete amaurosis occurs. One or both eyes may be affected, and total blindness, with gray atrophy, may remain as a permanent condition (Katayama and Okamoto; also Bayer). Experiments upon dogs indicate that the primary influence of the drug is on the ganglion-cells of the retina.

The icterus of *aspidium* poison has been attributed to the inflammation of the duodenum, but Grawitz, conceiving that it might be of hemic origin, found on examination of the blood of patients that immediately after the taking of large doses of the extract of male fern there was a marked lessening in the number of the red blood-corpuscles. Grawitz, therefore, came to the conclusion that the extract is powerfully destructive to the red blood-disks, and that the icterus was hemic in its etiology. C. Georgiewsky has found that in rabbits, fatally poisoned with male fern, no destruction of the red blood-corpuscles occurs if death takes place within twenty-four hours; but that if the symptoms be protracted over several days there is a very distinct lessening in the amount of hemoglobin in the blood; and that after death the characteristic change of the poisoning is a pronounced wide-spread deposit of ferrous pigments in the liver, the spleen, the marrow of the bones, and sometimes in the kidneys. In these later researches, the theory of Grawitz that the poison acts specially upon the liver-cells was not confirmed.

After fatal poisoning in the lower animals by *aspidium*, besides the granular pigmentation just spoken of, hemorrhagic gastro-enteritis and cystitis, with violent parenchymatous nephritis, may be found (Fröhner). The fatal result is partially due to violent irritation of the gastro-intestinal tract of the kidneys; but Quirll is probably correct in his belief that it is also largely the outcome of the influence

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\* *Aspidin* of R. Boehm (*Archiv f. Exper. Path. u. Pharm.*, 1896, xxxviii.) is distinct from filicic acid, and although poisonous both to frogs and to higher animals, appears not to be an active tanniacide.

of the poison upon the nerve-centres, to which factor should also be added its action upon the circulation. The minimum fatal dose of the oleoresin is hardly known, but eight grammes of the extract have caused death in a child about three years old; six drachms of the oleoresin have several times proved fatal in the adult: \* in Paltauf's case the fatal result is said to have been due to four and a half grammes.

**Therapeutics.**—Male fern is employed almost exclusively against the *tapeworm*. In its administration it is necessary to regard strictly the general rules applying with greater or less force to all anthelmintics, but which are especially imperative when a drug is employed against the tapeworm. The patient should live upon milk and a little bread for one day, and the following morning take a full dose—one-half to one fluidrachm (2–4 C.c.)—of the oleoresin, fasting, and repeating it in two or three hours. At noon the patient may eat freely, and in the evening a brisk cathartic should be given.

**PEPO.**—*Pumpkin Seed.*—The seeds of the ordinary pumpkin, *Cucurbita pepo*, are a valuable remedy in cases of *tapeworm*, perhaps even more efficient than the male fern, and perfectly harmless. Two ounces (62 Gm.) of the seeds may be beaten up with sugar into an electuary, or with water into an emulsion, and be taken fasting in the morning, the patient having dieted the previous day. Some hours after their administration a brisk purge should be given. I. G. Wolff asserts that the active principle is a resin, which he has found efficient in doses of fifteen grains (1 Gm.).

**KOUSO** (*Cusso*), *Brayera*, is the female inflorescence of *Hagenia abyssinica*, a tree of Abyssinia. It occurs in compressed greenish-yellow clusters, of a fragrant balsamic odor, and a taste which in a little while becomes acrid and disagreeable.

The crystalline resin *kosin*, discovered by Pavesi, is believed by Bedall to be the active principle of kousso. Leichsenring affirms it to be *kosotoxin*, an amorphous, yellowish-white substance, which, according to Handmann, is an active paralyzant to all muscles, including the heart, and also of the motor nerve-endings.

*Brayera* is a most efficient remedy against the *tapeworm*, and even in large doses causes no greater inconvenience to the patient than some nausea, abdominal pain, and looseness of the bowels. It is generally not necessary to administer any purgative with it, and the worm is discharged dead with the last watery passages. A half-ounce of the powdered flowers is given suspended in water in the morning, with the usual precautions as to diet. The best preparation is the yellowish-brown, impure, amorphous *kosin* of commerce, which may be given in doses of seven to fifteen grains (0.5–1 Gm.) repeated every half-hour until four doses have been taken, a full dose of castor

\* *Therap. Monatsch.*, 1889, iii.; *München Med. Wochen.*, 1890, xxxvii.; *Lancet*, 1882; *Deutsch. Med. Wochen.*, 1891, xvii.

oil being administered one hour later. Care should be exercised in giving brayera to pregnant women, as it is stated that it has produced abortion.

*Pomegranate Rind*.—The bark of the stem and root of the pomegranate (*Punica granatum*), although very unpalatable, is efficient against the *tapeworm*. As originally stated by C. Tanret, pomegranate bark contains four alkaloids; the most important are *pelletierine* (*punicine*) and *iso-pelletierine* (*iso-punicine*). The official pelletierine tannate is a mixture of the four alkaloids.

#### Official Preparations:

Fluidextractum Granati.....	30 minims (2 C.c.).
Pelletierinæ Tannas.....	4 grains (0.25 Gm.).

In the higher animals these alkaloids paralyze the peripheral motor nerves, having a curare-like action, without affecting sensation or muscular contractility. G. Coronedi agrees with the statement that the paralysis is peripheral, but believes that the muscles themselves are affected. The efficiency of pelletierine as an anthelmintic has been shown by Dujardin-Beaumetz and confirmed by various clinicians. Dujardin-Beaumetz also has employed it successfully in *Ménière's disease*, and states that hypodermic injections of six grains (0.4 Gm.) produce in man severe vertigo and muscular weakness, with great retinal congestion. We have seen five grains cause in the adult pronounced muscular weakness amounting almost to general paralysis, and a number of cases have been reported in which it has produced in infants symptoms so severe as to discourage its employment in patients of that class.\* Galezowski has used pelletierine in paralysis of the third and sixth pairs of nerves with asserted good results.

THYMOL has been used by Neuma Campi † for the destruction of *tapeworm*; he gives half an ounce of castor oil in the evening, in the morning two drachms (7 Gm.) of thymol divided into twelve doses, one to be taken every quarter of an hour, and twenty minutes after the last dose of thymol another dose of castor oil. Thymol is a specific against *hook-worms*—the *Ankylostoma* (*Uncinaria*) *duodenale* and the *A. (U.) Americana*. After starvation for twenty-four hours, a thirty-grain dose may be given and repeated in twenty-four hours, followed by a brisk purge, as suggested by F. M. Sandwith. Giddiness, fall of temperature from 1° to 2° C., slowness of the pulse and respiration, staggering, and even collapse are liable to occur; a cure is almost invariably effected by such doses, but probably smaller amounts would suffice.

OIL OF TURPENTINE, in doses of half a fluidounce, has been used in cases both of *tapeworm* and of *round-worm*. It is efficient, but is liable to produce unpleasant

\* See *Bull. de Therap.*, lxxviii., lxxx., cxi., July, 1886; also *University Med. Magazine*, i. 639.  
† *Il Raccoglitore Medico*, abstracted in *Buffalo Med. Journ.*, Oct. 1886.



effects, and should be employed only when other remedies have been used without success or are not to be had. It should be given in combination with twice its bulk of castor oil, or sometimes in smaller doses as an aid to other vermifuges.

**KAMALA.**—*Kamala*.—The glands and hairs from the capsules of *Mallotus Philippinensis* are used against the *tapeworm*. It is an orange-red, very inflammable, granular powder, mixing with water with some difficulty, and containing traces of a volatile oil and coloring resinoids, to one of which Anderson has given the name of *rotlerin*. Kamala is actively purgative, indeed drastic, and may cause nausea and vomiting. A tincture of it may be used. Dose of the powder, one to two drachms (4–8 Gm.) in syrup, given in the morning; repeat in ten hours if it does not purge.

**AZEDARACH**, the bark of the root of *Melia azedarach*, or Pride of China, is used in the South as a remedy for the *round-worm*. It is said to possess poisonous properties similar to those of *spigelia*, yet it is affirmed that animals and children eat its fruit with impunity. It is usually given in decoction (two ounces to one and a half pints, boiled to a pint), the dose being for a child a tablespoonful (15 C.c.) every two or three hours until the bowels are affected.

**ACIDUM PICRUM.**—*Picric* or *carbazotic acid*, on account of its corrosive character, is used internally exclusively in the form of the *ammonium picrate*, which, according to Erb, is rapidly absorbed and eliminated in the urine, and produces, in doses of fifteen grains, yellowness of the conjunctiva, skin and urine, often accompanied by gastric disturbances. Von Beck reports urticaria and measles-like eruptions produced by the long use of the drug; and Achard and Clerc have seen violent general erythematous swelling of the limbs produced by the local application of the solution of *yicric acid*.

According to Binz, *picric acid* acts similarly to but much less powerfully than does quinine upon infusoria. W. Erb found that a single dose of eight grains will produce in the rabbit falling temperature, weakness, diarrhœa, collapse ending in death, sometimes preceded by convulsions. The blood of animals slowly killed by the *picrate* was a dirty-brown color, with distinct nuclei in the red blood-disks and floating free in the serum. The alterations in the red blood-corpuscles occurred during life, and could be produced by mixing *ammonium picrate* with blood outside of the body. *Ammonium picrate* has been commended as an antiperiodic, but is of no value; nor does it seem useful as an anthelmintic or in *trichiniasis*. (See Erb.) Hammond declares that the salts of *picric acid* are specific in *exophthalmic goût*. According to Erb, the ammonia salt, nine to twelve grains a day, may be given with safety.

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## FAMILY III.—DIGESTANTS.

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IN this family are associated a few remedies which are used to aid the alimentary canal in dissolving the various articles of food.

### PEPSIN.

As is well known, there is secreted by the gastric glands a peculiar albuminous body, which has the power of dissolving, when in acid solution, coagulated and insoluble proteids.\* To this principle the name of pepsin has long been given. A discussion of its nature and properties would be more in place in a work on physiology than in one on therapeutics. *Pepsin* is required by the U. S. Pharmacopœia to be able to digest three thousand times its weight of freshly coagulated egg albumin.

Various processes have been suggested for the preparation of the drug, but none of them yields a pure proximate principle, if indeed pepsin have really such nature and be not an albuminous body of varying constitution.

The activity of pepsin is destroyed by a large number of substances. Among its known incompatibilities the most important from the standpoint of the practical prescriber are: Alcohol, alkalies, strong acids (more than one-half per cent. of hydrochloric acid), various metallic salts and tannic acid. Consequently we think the physician should eschew all elixirs or compound preparations of the drug, using only the powdered pepsin or a glycerite of pepsin, or a freshly prepared solution in water containing 0.2 per cent. of hydrochloric acid. If other remedies are to be given it is no great hardship to write a second prescription for them.

**Therapeutics.**—The value of pepsin in practical medicine is very questionable. It is very rarely lacking in the ordinary forms of gastritis or dyspepsia, the inactivity of the gastric juices in these cases being due to the absence of hydrochloric acid. Moreover, the doses in which it has been given and the methods of its exhibition have generally been such as to make it certain that any beneficial effects following its administration were due to some other cause than the pepsin.

The value of pepsin has been overestimated, and it has been given to adults in ridiculously small doses: at least half a drachm (2 Gm.) of the ordinary commercial article should be exhibited at a dose.

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\* The milk-curdling ferment of gastric juice and of rennet is not pepsin.

## PANCREATIN.

Pancreatin has been used to considerable extent as a digestant and is recognized by the U. S. Pharmacopœia. It is highly improbable, however, that it can exercise any beneficial influence upon the digestive processes, as Sollmann has shown that a mixture of one-tenth per cent. hydrochloric acid and pepsin completely destroys its digestive properties. Of the numerous concoctions which are largely exploited by their proprietors, and professed to contain both panereatin and pepsin, it seems hardly necessary to speak were it not for the fact that they are so widely employed in medicine. It is absolutely impossible that they can contain both of these active ferments, and it is probable that they contain neither. Pancreatin, however, has a place in medicine for the preparation of *predigested foods*.

It must be remembered that most peptones have a distinctly bitter taste and therefore thoroughly digested foods are very unpalatable. The bitterness may be partly concealed by the addition of aromatic flavoring extracts, but more commonly it is the custom to arrest the process of digestion before it is complete.

At first thought pepsin would appear to be the most available ferment for the preparation of peptones; but practical experience has led to reliance upon pancreatin. Pancreatin, pancreatic extracts, and pancreatic liquors are now found abundantly in commerce. The superiority of the secretion of the pancreatic gland as a practical ferment is connected with the fact that it contains two distinct classes of digestive principles,—namely, pancreatic diastase, which dissolves starch, and trypsin, which acts upon albuminous principles. It is of great importance to be able to determine readily the value of any preparation of pancreatin. The test devised by William Roberts (*Digestive Ferments*, London, 1881) appears to be very practical. If pancreatin be added to fresh milk without an alkali, in the course of a few minutes the liquid acquires the property of curdling abundantly upon boiling; and Roberts estimates the value of a pancreatin by the number of cubic centimetres of milk which are transformed by one cubic centimetre of the sample at a temperature of 40° C. to the curdling point in five minutes. A test which may be substituted for that of Roberts, and which is especially applicable to the ordinary pancreatic extracts or so-called pancreatin, is based upon the peptonizing power of the powder. Five grains of it added to twenty grains of sodium bicarbonate should so alter the casein contained in one pint of milk at a temperature of 115° F. in an hour, that no coagulation will occur upon the addition of nitric acid.

To make *peptonized milk* add 5 grains of pancreatin and 20 grains of sodium bicarbonate to a pint of milk, at a temperature of about 100° F. Digestion will be complete in one hour or one hour and a half. If the bitter taste which is developed is seriously objected to, the digestive action may be stopped at the end of a half hour by heating the milk almost to the boiling point.

To make *peptonized gruel* prepare a thick gruel with arrow root, oat meal or other farinaceous article, add while still heated an equal quantity of milk and when cooled to about 100° F. 5 grains of pancreatin and 20 grains of sodium bicarbonate to each pint of the mixture. Digest at blood heat for two hours. Raise to boiling point and then strain.



To make *peptonized beef tea*, simmer half a pound of minced beef for two hours in a pint of water containing twenty grains of sodium bicarbonate, allow to cool to about 100° F., digest at this temperature with a tablespoonful of liquor pancreaticus or ten grains of pancreatic extract for three hours, decant and momentarily boil. This beef tea is said to be about equivalent to milk in nutritive value, containing 4.5 per cent. of organic solids, three-fourths of which is peptone.

### MALT.

Malt is the seeds of ordinary barley caused to enter the incipient stage of germination by artificial means and dried. It is prepared by soaking the grains in water and leaving them in heaps in a room of moderate temperature, and by occasional turning preventing the heat given off during the process of germination from accumulating; then finally killing the germ with heat. The color varies from pale amber to black, according to the degree of the heat used in drying. There is formed during germination a peculiar ferment, *diastase*, which is able to convert starch into dextrin and glucose. The *EXTRACTUM MALTI* of the U. S. Pharmacopœia is made by rapidly evaporating an infusion of malt to the consistency of a thick, honey-like liquid at a temperature not above 130° F. It should contain practically all the diastase of the malt. The odor of the extract of malt is slight and peculiar, the taste sweet, and the reaction to paper distinctly acid. It dissolves freely in water, and is precipitated by alcohol, tannic acid, mercuric chloride, and various other metallic salts. Commercial malt extracts vary greatly: some of them are practically preparations of glucose, others are of the nature of strong or weak beers; true extract of malt contains no alcohol at all. There are also on the market a number of more or less pure preparations of diastase; the better of these are much more eligible preparations.

**Therapeutics.**—R. H. Chittenden and G. W. Cummins have found that diastase acts better in a neutral than in an alkaline solution; that proteid matters when present in the alkaline solution prevent the retarding influence of an alkaline carbonate; that neutral peptone exerts a direct stimulant effect on the amylolytic action, but that the greatest amylolytic action is observed in the presence of proteid matter partially saturated with acid, although a larger percentage of acid-proteids may cause complete destruction of the ferment. These results seem to prove that diastase, when taken into the stomach, must sooner or later be completely destroyed by the gastric juice, and that in order for it to have any distinct effect upon digestion it must be given at the beginning of the meal. In *cancer* of the stomach and other diseases in which the gastric juices lack acidity, the action of diastase upon starch must be more pronounced; but unfortunately the failure of the starch-digestion is usually associated with gastric hyperacidity.

PAPAIN.—The *Carica Papaya* is an herbaceous tree universally cultivated in tropical countries for its fruit, the papaw, the juice of which yields a peculiar ferment, to which the name of *papain* was given by Wurtz; it is now also known by the name originated by Pekolt, *papayotin*. This substance is a ferment, which has the power of dissolving fibrin, muscular fibres, tissues, etc. Its action on albuminoids is said to resemble that of trypsin rather than that of pepsin. (See Martin.)

Papain has been used in medicine as a substitute for pepsin, in doses of five to ten grains (0.3–0.6 Gm.). It has also been very highly recommended for the purpose of destroying organic tissues of low type, as in *diphtheria* (A. Jacobi), in the thickening of chronic *eczema*, in *warts*, and in *pyogenic membranes* surrounding old sinuses or abscesses. It is not caustic, but simply dissolves the diseased tissues, and is said to cause no pain.\* It should be applied, one part each of papain, glycerin, and water. In our laboratory experiments commercial papain of the most esteemed brands has failed to exert any solvent power over albuminous substances, and it is probably a remedy of little value.

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## FAMILY IV.—ABSORBENTS.

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THIS class contains remedies which are used for the purpose of absorbing acrid and deleterious materials, such as offensive discharges on the exterior of the body, and acrid secretions, or the irritant products of the partial decomposition of food, in the alimentary canal. For the first purpose very fine dry earth and plaster of Paris are used to some extent in practice; but, as their employment is purely within the province of the surgeon, we shall say no more about them here.

### CHARCOAL.

Charcoal is official in the U. S. Pharmacopœia in two forms:

CARBO LIGNI.—*Charcoal* prepared from wood.

CARBO ANIMALIS.—*Animal Charcoal*, prepared from bone.

Charcoal for medicinal purposes should be made out of a light, porous wood: that prepared from the young shoots of the willow or of the poplar is almost exclusively employed. It is a black, brittle substance, and should have more or less lustre. It has a very remarkable power of absorbing many times its own bulk of gases, and, when exposed to the air, increases rapidly in weight. It should, therefore, when intended for medicinal purposes, be powdered as soon as it is burnt, and put in small, completely-filled, closely-sealed bottles.

Animal charcoal, or *bone-black*, formed as it is by the partial burning of bones, contains a large percentage of calcium phosphate and carbonate. *Purified Animal Charcoal* (CARBO ANIMALIS PURIFICATUS) is prepared by removing the lime salts by dilute muriatic acid.

**Therapeutics.**—Internally, charcoal is employed as an absorbent in fermentative intestinal *dyspepsia*, *cardialgia*, and similar disorders. As moist charcoal is not an absorbent, it is evident that it is of very little value; its habitual employment is generally combined with that of laxatives for fear of accumulation in the alimentary canal. Dose of charcoal, from one to two drachms (4-8 Gm.). Except in a mechanical way, it is perfectly innocuous in any dose.



## FAMILY V.—DISINFECTANTS.

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DISINFECTANTS are agents which are used for the purpose of preventing the growth of bacteria. This may be accomplished in two ways,—either by killing the germs (germicides) or by rendering the media unfavorable for the growth of the micro-organisms (antiseptics). All chemical germicides become, however, when in dilute solution, antiseptic, so that the natural division of these agents, as given above, does not serve well as a basis of a classification for systematic study. Disinfectants may be conveniently divided into forces, and material chemical groups as follows:

I. *Forces*; heat and cold.

II. *Metallic salts*, including certain salts of mercury, silver, copper, zinc, and iron.

III. *Halogens*, including chlorine and the hypochlorites, iodine, bromine, fluorine and their various compounds.

IV. *Oxidizing disinfectants*, including especially hydrogen dioxide and potassium permanganate.

V. *Carbon compounds*, including phenol, cresylic acid, creosote, salicylic acid, benzoic acid, thymol, menthol, alcohol, formaldehyde, the volatile oils and allied drugs.

VI. *Sulphur and Boron derivatives*, including especially sulphurous acid, boric acid, and their salts.

### I.—COLD AND HEAT.

*Cold*.—The effect of low temperature in preventing the growth of micro-organisms is well known and daily taken advantage of by the housewife in the preservation of foodstuffs. Very few bacteria will multiply at a temperature lower than 40° F. On the other hand, cold cannot be considered as a germicidal agent, for it has been shown that even the extraordinarily low temperature of liquid air does not destroy the vitality of the typhoid bacillus and other test organisms.

*Heat*.—As a germicide fire is absolutely efficient, but destructive. The lower degrees of heat have been used without moisture (dry heat), and with moisture (moist heat).

Moist heat is much more efficient than is dry heat.

According to Sternberg, while most micro-organisms are destroyed in the presence of moisture by a temperature of 62° C. (143° F.), certain of the more resistant species of bacteria will withstand a heat considerably higher than this; but all bacteria free from spores are destroyed by the heat of boiling water in one to two minutes. On the other hand, some spores are able to withstand boiling water for several hours. To destroy with certainty all forms of life requires, according to

Sternberg, an exposure to moist heat of a temperature of 115° C. (239° F.) for half an hour. This temperature can of course be produced only under pressure. The most satisfactory manner of using this method of sterilization is by means of the *autoclave*, an apparatus so arranged as to prevent the escape of the steam until the pressure within the autoclave has reached nine to ten pounds, at which time the temperature will approximate 115° C.

Dry heat is much inferior in its germicidal effect to moist heat.

Wolf found that dry air at 140° C. was scarcely more destructive than is watery vapor at 100°; Koch, that five minutes' exposure to steam was equal to an hour or an hour and a half with the dried air. The results reached by Koch and Wolff-hügel are in accord with other evidence, and may be considered correct. They are as follows:

1. A temperature of 100° C. (212° F.), dry heat, maintained for one hour and a half, will destroy bacteria which do not contain spores.
2. Spores of mould-fungi require for their destruction in hot dry air a temperature of from 110° to 115° C. (230°–239° F.) maintained for one hour and a half.
3. *Bacillus*-spores require for their destruction in hot air a temperature of 140° C. (284° F.) maintained for three hours.
4. In dry air the heat penetrates objects so slowly that packages, such as pillows or small bundles of clothing, are not disinfected after an exposure of from three to four hours to a temperature of 140° C. (284° F.).
5. Exposure to a temperature of 140° C. (284° F.) in dry air for a period of three hours injures most objects requiring disinfection (clothing, bedding, etc.) to a greater or less degree.

George H. Rohé found that rolls of blankets exposed in a chamber heated to 280° F. for three hours were very slightly affected in their interior. This is in strict accord with the teaching of Parsons and Klein, of the London Local Governing Board, and of other observers.

Dry heat is so inferior to moist heat that it is at present never employed as a germicide. Quarantine and other health stations are or ought to be supplied with apparatus for exposing infected articles to the prolonged action of hot steam in chambers, etc. For ordinary household purpose, however, the physician is forced to rely upon boiling, which, when maintained for thirty minutes, may be considered as practically efficient.

## II.—METALLIC SALTS.

MERCURY.—All of the salts of mercury appear to have more or less germicidal properties. The most powerful of them are the bichloride and the biniodide. The bichloride of mercury has long been recognized as one of the most powerful germicides known.

In 1870 John Dougall announced that corrosive sublimate, 1 part in 6500, would kill spermatozoa, and 1 part in 6000 infusoria; the later researches of Koch, Jalan de la Croix, and Sternberg have confirmed this result, and shown that corrosive sublimate is one of the most powerful of known germicides. Micrococci and bacilli in active growth without spores are killed by solutions of 1 in 20,000, while solutions of 1 in 1000 will rapidly destroy the spores of *B. anthracis* and *B. subtilis*. Results contrary to these have, it is true, been obtained by Klein, of London, who asserts that a one-per-cent. solution of the mercuric chloride is no more a germicide than vinegar; but the evidence to the contrary is so strong that it seems almost a certainty that there was some error in Klein's experiment. According to the detailed

experiment of Koch, the spores of *B. anthracis* are absolutely incapable of germinating in a proteid solution if as little as 1 part of corrosive sublimate in 300,000 be present. Sternberg has confirmed the experiments of Koch.

It must be remembered that corrosive sublimate is so readily decomposed by ammonia and other substances usually present in a mass of filth that it is not available for disinfectant purposes on a large scale; even when the amount of organic matter is small, the usefulness of corrosive sublimate is often destroyed by its chemical instability: thus, it should not be employed for the destruction of germs in fecal discharges. A standard solution of 1 part in 1000 may be used for bedding, which can be soaked in it, for washing the floors and walls of infected apartments, and for disinfecting the hands of surgeons and gynecologists. After the corrosive sublimate has done its work it should be removed by free washing with pure water. Even in the cases just spoken of corrosive sublimate is often inferior to formaldehyde.

For various surgical purposes the sublimate may be used in strengths varying from 1:2000 to 1:10,000. It is well to add to the solutions of corrosive sublimate an equal quantity of ammonium chloride or else a small proportion of tartaric or hydrochloric acid, as these substances lessen the liability to precipitation.

The *biniodide of mercury* (*hydrargyri iodium rubrum*), although not nearly so widely employed as the bichloride, seems to be even more active as a germicide. According to the experiments of Burgess, a 1:5000 solution of the biniodide is equivalent in strength to a 1:2000 solution of the bichloride. Sternberg has found that a 1:20,000 solution of the biniodide is equivalent to 1:15,000 solution of the bichloride of mercury.

The probable reason why the mercuric iodide has not come into use as a germicide is the fact that it is almost insoluble in water. It may be readily dissolved, however, by the addition of potassium iodide or lithium iodide to the solution. Rosenberger and England suggest the double *lithium mercuric iodide*, which is freely soluble in water, is not precipitated by the fixed alkalies, and according to their experiments is actively germicidal.

**SILVER.**—The salts of silver rank next to the salts of mercury as the most powerful germicides we possess. According to Miquel, silver nitrate\* prevents the growth of atmospheric germs when present in the proportion of 1 part to 12,500. According to Boer, a 1:4000 solution destroys typhoid bacillus in two hours, but it required a 1:2500 solution to kill the diphtheria bacillus in the same time. Behring found that a 1:10,000 solution is capable of destroying the anthrax spores in forty-eight hours.

Unfortunately, the silver nitrate is an extremely unstable salt, being decomposed by the alkalies, the mineral acids, albumin, and even decomposing in the air on exposure.

Various other less active *metallic salts* have been used in the past as disinfectants but are of very little practical value, and have been superseded by the numerous active modern germicides. Many of

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\* For consideration of various non-official preparations of silver see p. 319.



these salts act chiefly by the capability which they have of taking sulphur away from sulphuretted gases, and thereby lessening odor; so that they are rather deodorants than disinfectants. The most used of these disinfectants are the *zinc sulphate*, *zinc chloride*, and *lead nitrate*, the latter forming the basis of the so-called *Ledoyen's Disinfectant Solution*. They should, all of them, be totally disregarded. Old iron, and the impure *ferrous sulphate* (*Copperas*), have to some extent resisted modern innovation, and have been believed to have the power of oxidizing organic matter and of attacking disease germs, which makes them of value. Of the two, copperas is certainly the more efficacious; but in an official study Dr. A. J. McLaughlin has shown that it has no dominant influence over putrefactive changes unless present to the extent of five per cent.—that its saturated solution does not affect pathogenetic organisms, and that the same solution mixed with half its bulk of feces fails to disinfect the mass after three days.

### III.—HALOGENS.

#### CHLORINE.

Chlorine is a yellow gas, extremely irritant to all mucous membranes with which it may come in contact. Its solution in water (*Liquor Chlorig Compositus*) is recognized by the pharmacopœia. More commonly it is generated extemporaneously when required, by the decomposition of a hypochlorite. Two of these are official.

#### Official Preparations :

Calx Chlorinata [Bleaching Powder]. . . . .	Not used internally.
Liquor Sodæ Chlorinatæ [Labarraque's Solution]. . . . .	$\frac{1}{2}$ to 2 fluidrachms (2-8 C.c.).
Liquor Chlorig Compositus. . . . .	$\frac{1}{2}$ to 2 fluidrachms (2-8 C.c.).

CHLORINATED LIME or *Bleaching-powder* (often incorrectly called chloride of lime) is a grayish-white substance occurring in powder or friable lumps, having a hot, acrid, astringent taste, and an odor resembling that of chlorine. It is made by the action of chlorine upon calcium hydrate, or slaked lime, and should contain at least thirty per cent. of available chlorine. It probably varies in its chemical constitution, but, according to the most recent views, is chiefly composed of the calcium hypochlorite and chloride. When exposed to the air it slowly evolves hypochlorous acid, which, being an unstable compound, undergoes spontaneous decomposition, and finally sets free fourteen-fifteenths of its chlorine. When an acid is added to chlorinated lime, the chlorine gas is rapidly evolved. If a specimen of bleaching-powder be very moist, it generally contains an over-proportion of the deliquescent calcium chloride, is correspondingly unable to liberate chlorine and is therefore of inferior value.

SOLUTION OF CHLORINATED SODA, *Labarraque's Solution*, is made by triturating chlorinated lime with a solution of sodium carbonate. It is a greenish-yellow liquid, having a slight odor of chlorine and a

sharp saline taste. It contains, among other substances, sodium hypochlorite, and possesses the therapeutic and disinfectant properties of the chlorinated compound. Owing to its liquid form, its comparative freedom from odor, and its depositing sodium chloride on evaporation, it is the most elegant of all the chlorine preparations for use in the sick-room.

COMPOUND SOLUTION OF CHLORINE, which replaces the old *chlorine water*, is made by adding hydrochloric acid to a solution of potassium chlorate, and should contain 0.4 per cent. of chlorine with some chlorine peroxide.

When chlorine is brought into contact with organic substances and moisture, it unites with the hydrogen of the water and liberates nascent oxygen, which rapidly oxidizes and destroys the organic compound. When chlorine comes in contact with sulphuretted hydrogen, it removes its hydrogen and thereby destroys it. On account of its destructive action on organic matter, its being extremely obnoxious to animal life, and its comparative expensiveness, chlorine gas is at present never used to disinfect rooms, ships' holds, or similar places. Inspired in sufficient amount, chlorine gas produces, both in man and in the lower animals, narcotism, and finally death from paralysis of the respiratory centre.\* The germicidal influence of chlorine is very great.

Fisher and Proskauer found that dried anthrax spores maintained their integrity for one hour when exposed to the action of a dry chlorine atmosphere containing 44.7 parts of chlorine in 100; but when the air and the spores were moist, one hour's exposure to an atmosphere containing four per cent. of chlorine produced complete disinfection. If the exposure were continued for three hours, one per cent. of chlorine was an efficient germicide; and if the spores were exposed for twenty-four hours, the effective proportion of chlorine could be still further reduced. In Sternberg's experiments, six hours' exposure of vaccine lymph dried upon ivory points to an atmosphere containing 1 part of chlorine in 200 was sufficient to destroy the infective property of the lymph, while the bacteria of putrid urine were destroyed after six hours' exposure to an atmosphere containing 1 part of chlorine in 400. Klein also found that after the compartment of a stable in which pigs had died of swine-plague had been thoroughly fumigated for six hours with chlorine, healthy animals could be placed therein with safety.

The result of all our knowledge upon the subject of the disinfectant properties of *chlorine*, *iodine*, and *bromine* has been summed up by George H. Rohé as follows:

1. *Chlorine* is an efficient disinfectant when present in the proportion of 1 part in 100, provided the air and the objects to be disinfected are in a moist state and the exposure continues for upwards of an hour.

2. *Chlorine*, when used in sufficient concentration to act as a trustworthy disinfectant, injures colored fabrics and wearing apparel.

3. *Bromine* is an efficient disinfectant in the proportion of 1 part in 500, provided the air be in a moist state and the exposure continues for upwards of three hours.

4. *Iodine*, in solution, is an efficient disinfectant in the proportion of 1 part in 500, the exposure continuing for two hours.

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\* Consult Arch. f. Exper. Path. u. Pharm., xiii.

5. The use of chlorine, and in a greater degree of bromine, requires considerable experience in management: when carelessly handled these elements may cause inconvenient or even dangerous symptoms in persons using them; hence they are not suitable as disinfectants for popular use.

The experiments of J. R. Duggan indicate that the hypochlorites are among the very best of our practical germicides. He found that 0.25 of one per cent. (1 part to 400) of chlorine as hypochlorite is an effective germicide even when allowed to act for only two minutes; while 0.06 of one per cent. (6 parts to 10,000) will kill the spores of *B. anthracis* and *B. subtilis* in two hours.

According to Duggan, a two-per-cent. solution of *sodium hypochlorite*, representing six per cent. of available chlorine, will kill the anthrax spores in thirty minutes. Sternberg found that it required seven per cent. of a *commercial* Labarraque's solution to kill the anthrax spores in two hours. It must be remembered that the commercial preparations of both chlorinated lime and chlorinated soda vary enormously in strength. The Committee on Disinfection of the American Public Health Association, 1885, found that commercial specimens of *Liquor Sodæ Chlorinatæ* varied in the amount of available chlorine from 3.8 to 0.01 per cent. and chlorinated lime from 33.5 to 24.1 per cent. of available chlorine.

**Therapeutics.**—Bleaching-powder usually contains from twenty-five to forty per cent. of available chlorine. For most purposes, a solution made with 1 part of this preparation to 100 parts of water is strong enough, for it will contain from 0.25 to 0.04 of one per cent. of chlorine as hypochlorite. As is stated above, the smaller of these quantities is sufficient to destroy spores almost instantly. There are very few purposes to which disinfectants are applied that are not fulfilled by this solution of 1 to 100 of bleaching-powder. It is not dangerously poisonous, is said not to injure (although of course it bleaches) the fibre of clothing, bedding, etc., and is very cheap, since it is worth only about five cents per pound. *For the destruction of disease-germs in urine, fecal discharges, sputum, etc., a saturated solution of bleaching-powder appears to be in all respects the best disinfectant known: for the purification of cesspools, sewers, or similar receptacles, or of masses of infected filth, chlorinated lime stands at the head of known germicides.\**

*Internally* chlorine has been used in various diseases, especially in

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\* There are not many affairs in life in which the public have been so superabundantly fleeced as in the matter of disinfection. A most extraordinary part of this swindling is the ease with which distinguished members of the medical profession have given certificates of efficiency and value to comparatively inert and extraordinarily expensive proprietary compounds. Oddly enough, the cat that has drawn the chestnuts out of the fire for avaricious manufacturers has not even had the sense to smell the odor of its own paws when burning! There is no proprietary disinfectant whose value corresponds with its selling price.

H. C. Wood, Jr., compiled for the 12th edition the following table on the basis of one cent's worth of corrosive sublimate.

Name.	Full Cost.	Name.	Full Cost.
Mercury bichloride.....	\$0.01	Creolin.....	\$0.50
Chlorinated lime.....	0.00½	Platt's chlorides.....	3.19
Cresol.....	0.06	Sanitas.....	11.72
Bacillol.....	0.24	Listerine.....	62.81
Lysol.....	0.23		



malignant *typhus*, but at present is rarely if ever so employed. It is occasionally used as an intestinal antiseptic in *enteric fever*. It is stated to be stimulant and tonic to the stomach, and is thought by some to have an especial influence upon the liver. It has been employed in *chronic hepatic affections*; either the compound solution of chlorine or the solution of chlorinated soda, properly diluted, may be employed. Chlorine water is a powerful irritant, capable of producing severe inflammation of the skin or toxic *gastro-enteritis*. Properly diluted, it forms an excellent stimulant, disinfectant, detergent wash for *foul ulcers*, and may be used as a gargle in *malignant sore throat*.

**FLUORIDES.**—Hydrofluoric acid gas, dissolved in water,—i.e., *commercial hydrofluoric acid*,—is a powerful corrosive which hardens the skin or tissue with which it comes in contact and continues to penetrate, producing great pain. It is not itself used at all in medicine, and is probably unfit for any therapeutic purposes.

According to Tappeiner and to Waddell, the alkaline fluorides are not extremely irritant, and when taken in doses of from one to one and a half grains are depressants to the circulation, especially affecting the vaso-motor centres. They have been used to some extent in various diseases, but have given no promise of usefulness unless it be in the treatment of *goitre*.

As germicides the fluorides have been used in various forms. Under the name of *Fluorol*, the *sodium fluoride* has been employed in a two-per-cent. solution for the treatment of infected wounds. The *silver fluoride*, *Tachiol*, is a feeble coagulant of albumin, but is affirmed by Durante and Perez to be in 1:1000 an effective, very penetrating, not pronouncedly irritant, germicide which may be used in various local affections.

Recently, various *organic fluorides* have been put upon the market. According to Tischer and Beddies, they are antispasmodics and bactericides.

*Di-fluor-diphenyl*, a white aromatic powder, insoluble in water, freely soluble in alcohol, has been recommended as a ten-per-cent. dusting-powder or a ten-per-cent. ointment, by J. Thimm in the treatment of *syphilitic ulcerations*. Its five-per-cent. ointment has been exploited as *Antitussin*, as useful when applied locally in whooping-cough.

*Neodermin* is a five-per-cent. ointment of fluor-pseudocumol, said to act like *Antitussin*.

*Fluoroform*, affirmed by Binz to have properties somewhat similar to chloroform, has been put upon the market under the name of *Fluoroformol*, in the form of a two- and eight-tenths-per-cent. aqueous solution, which is almost odorless and tasteless, and is said to be non-toxic and non-irritant. It has been used in internal *tuberculosis* in doses of one drachm four or five times a day, but, according to Gori, is of very little value.

The following table was compiled some years since by A. W. Harlan, of Chicago. The cost represents the same germicidal power. In comparing these tables it should be remembered that the constitution of some of these proprietary disinfectants has entirely changed.

Name.	Full Cost.	Name.	Full Cost.
Corrosive sublimate.....	\$0.00 $\frac{1}{16}$	Corrosive sublimate.....	\$0.00 $\frac{1}{16}$
Chlorine.....	.01 $\frac{1}{2}$	Thymic acid.....	4.80
Copper sulphate.....	.01 $\frac{1}{2}$	Little's sol. phenyl.....	13.00
Mercury binoiodide.....	.02 $\frac{1}{2}$	Fifty per cent. chlor. zinc, Squibb's.....	35.00
Mineral acids.....	.02 $\frac{1}{2}$	Feuchtwanger's disinfectant.....	35.00
Bromine.....	.08	Phénol sodique (Hance Bros. & White).....	51.00
Chloroform.....	.14 $\frac{1}{2}$	Platt's chlorides.....	66.00
Potassium chlorate.....	.16 $\frac{1}{2}$	Girondin.....	80.00
Silver iodide.....	.20	Williamson's sanitary fluid.....	80.00
Picric acid.....	.20 $\frac{1}{2}$	Bromo-chloralum.....	80.00
Iodine.....	.21 $\frac{1}{2}$	Blackman's disinfectant.....	96.00
Silver nitrate.....	.22 $\frac{1}{2}$	Squibb's solution impure phenol.....	112.50
Potassium permanganate.....	.30 $\frac{1}{2}$	Burchardt's disinfectant.....	182.50
Carbolic acid.....	.34 $\frac{1}{2}$	Phénol sodique, French.....	255.00
Benzoic acid.....	.56	Listerine.....	495.00
Salicylic acid.....	.69		

## IV.—OXIDIZING DISINFECTANTS.

## POTASSIUM PERMANGANATE.

This salt occurs in slender, prismatic crystals of a dark purple color, inodorous, of a sweetish, disagreeable taste, and forming with water a solution varying from a purplish black to a beautiful reddish lilac, according to the strength. When kept dry, and not exposed to the atmosphere, potassium permanganate is a permanent salt, but whenever in solution it is brought into contact with an organic body it at once gives up its oxygen to the latter and is converted into potassa and black manganese oxide.

The statements concerning the germicidal power of potassium permanganate differ very materially.

Sternburg, in one series of experiments, found that 0.12 per cent. solution would kill the pus cocci in two hours and was equivalent to 0.8 per cent. solution of phenol. In a second series of experiments the same author found that it required a two-per-cent. solution to destroy the infection of mouse septicemia as compared with a 1.2 per cent. solution of carbolic acid. According to Koch, a five-per-cent. solution will destroy the anthrax spores in one day.

The difference in the results of experimenters has been shown by Sternberg to depend upon the amount of organic material present: when this is large, the salt is so rapidly destroyed by the organic material that it has no chance to act upon the contained micro-organisms.

**Therapeutics.**—Potassium permanganate affords a very elegant disinfectant and germicidal wash for *wounds, ulcers, abscesses, fetid ozæna, otorrhæa, leucorrhæa*, etc. In dilute solution its local influence is stimulant and beneficial. When employed in the form of powder it even affects living tissues, acting as a mild caustic, and, as such, may often be applied with advantage to *sloughing ulcers*. As a wash, the strength may vary from one to twenty grains to the ounce.

P. W. MacDonald has found the potassium permanganate to be very effective in *dysentery*. As soon as the diagnosis is reached, the whole of the lower intestine should be washed out, night and morning, with a solution of potassium permanganate (from two to four grains to a pint).

The injection of a strong solution of potassium permanganate in the immediate neighborhood of *snake-bites* is said to be very effective. The action of the permanganate in these cases is that of a destructive oxidizant.

In a series of laboratory experiments we have determined that potassium permanganate is capable of destroying many alkaloids, acting very rapidly upon cocaine and morphine, but slowly upon strychnine, and Fodera has found it antidotal also to helleborein and veratrine. We have also found that, as was first pointed out by William Moor, administered shortly after the alkaloid it is of prac-

tical value in morphine-poisoning. These results are in accordance with those obtained by other experimenters, and with numerous recorded cases of opium-poisoning.\* The permanganate should be given in small doses by the mouth at intervals during the acute stage of opium-poisoning, as it has been shown that there is a continuous excretion from the walls of the stomach of morphine, which is subsequently reabsorbed either from the stomach or intestines.

### HYDROGEN DIOXIDE.

The official Solution of Hydrogen Dioxide (Aqua Hydrogenii Dioxidii) is a colorless, odorless, slightly acid, aqueous solution of hydrogen dioxide ( $\text{H}_2\text{O}_2$ ) containing, when freshly prepared, about three per cent., by weight, of the pure dioxide, corresponding to about ten volumes of available oxygen; a small amount of free acid † is always left in it as a preservative. It is apt to undergo decomposition, and should be kept in a cold place, and not too tightly stoppered, particularly in hot weather, lest there should be such a brisk evolution of oxygen in a confined space as to cause an explosion. Hydrogen dioxide has been employed to a considerable extent in the arts for bleaching and cleansing human hair, engravings, very fine textile fabrics, etc.

The original statement of B. W. Richardson, that hydrogen dioxide is a powerful oxidizant of organic matters, is undoubtedly correct. It is an active coagulant of albumin, and when brought in contact with mucous membranes or ulcerated surfaces evolves gas, at the same time forming a dense white coating. With pus it effervesces very actively, and rapidly destroys the corpuscles, which immediately become granular, lose their shape, and break up into detritus. It is also a powerful deodorant, quickly oxidizing hydrogen sulphide and similar gases. Further, it is a very powerful germicide.

Pane states that he has demonstrated that hydrogen dioxide in a solution of 1 to 100 has an energetic germicidal power, and that solution of  $\text{H}_2\text{O}_2$ , in nutritive substances, 1 to 352, not only impedes the development, but after some days kills the spores of the bacillus of charbon. Sternberg, however, believes the germicidal value of hydrogen dioxide has been greatly overestimated. He experimented with a solution of hydrogen dioxide containing 4.8 per cent. of  $\text{H}_2\text{O}_2$  and five per cent. of sulphuric acid. In his experiments this solution in the strength of twenty per cent. (representing 0.8 per cent.  $\text{H}_2\text{O}_2$ )

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\* Moor (*Therapeutische Monatshefte*, 1903, vol. xvii., page 562) asserts that potassium permanganate forms with albumin a substance which has the power of destroying morphine, and concludes, therefore, that the permanganate is capable of following and neutralizing the poison in the blood. The chemical evidence, however, of his conclusions is not satisfactory, and we have found that the hypodermic injection of the permanganate in the lower animals does no good whatsoever in morphine-poisoning. Fodera asserts that the hypodermic injection of potassium permanganate has a certain antidotal value to morphine and strychnine even when injected at a distant point, but that if the alkaloid is injected before the potassium permanganate, the antidote has no effect upon the course of the poisoning.

† The existence of this free acid endangers the teeth when the Hydrogen Dioxide Solution is used habitually as a tooth-wash.



killed the anthrax spores in two hours, and ten per cent. of this solution destroyed the pus cocci in the same time: these effects Sternberg believes were largely due to the sulphuric acid, which he has found will destroy the pus cocci in two hours in proportion of 1:200. On the other hand, Gifford found that an almost neutral fifteen-per-cent., by volume, solution of hydrogen dioxide (about four per cent. by weight) destroyed the anthrax spores in five minutes and the pus cocci in one to two minutes. This solution diluted with four parts of water (0.8 per cent.  $H_2O_2$ ) failed to kill the pus cocci in thirty minutes. Gifford asserts that the bactericidal effect of hydrogen dioxide does not depend upon the liberated oxygen, and that the presence of large amounts of organic matter rapidly decomposes the agent and interferes with its germicidal properties.

**Therapeutics.**—The cost of hydrogen dioxide is entirely too great to permit the use of it as a general antiseptic, or, as has been proposed, for the purification of water. On the other hand, for some of the purposes of the surgeon it is invaluable, its liquid form making it especially adapted to the cleansing and disinfection of *putrid cavities*, deep infected *wounds*, *abscesses*, etc. Its influence is always immediate and fugacious, so that it cannot replace other antiseptics for the permanent dressing of wounds. Theoretically, it is capable of being used for the disinfecting of hands and instruments.

As a local application in specific *inflammations of mucous membranes* hydrogen dioxide is of the greatest value. In *scarlet fever* and *diphtheria* the official solution may be applied by mop to the pharynx, often with extraordinarily good results. Diluted one-half, it may be injected into the nasal cavities when they are affected. Injection of a solution of from twenty per cent. to full strength has received commendation in the treatment of *gonorrhœa* and *chancre*. The official solution has also been used with alleged great success as a local styptic. As a local application to mucous membranes, the official solution may be used; the stronger solutions are sometimes too irritating.

As an internal remedy, hydrogen dioxide was strongly recommended by John Day in *diabetes*, *low fever*, and other *typhoid* conditions. On account of its non-absorbability, however, it is probably of no value as a systemic remedy in these or any other diseases.

In H. C. Wood's experiments hydrogen dioxide was found, when injected intravenously, to produce immediate wide-spread coagulation of the blood; and put into the stomach in solution it must destroy itself by acting upon the organic contents and secretions. It is certain that death has been caused both in the lower animals and in man by injecting the solution into the pleural or peritoneal cavity. It has seemed to us probable that these deaths were due to shock, the outcome of the intense local irritation of the pleura or peritoneum, but the cases reported by E. G. Janeway suggest that they have been caused by embolic arrest of circulation in the nerve-centres.

In the case reported by Lauch, six injections into the pleural cavity, each containing 0.8 cubic centimetre of a three-per-cent. solution of hydrogen dioxide, were administered, but at the seventh the patient complained of faintness, the pulse failed, respiration became oppressed, and death occurred in ten minutes. In E. G. Janeway's case collapse with temporary hemiplegia followed immediately upon the injection of hydrogen dioxide into a sacculated empyema. It must be remembered, however, that there are on record a number of cases in which injection of simple water into the pleura has produced collapse, paralysis, or convulsions; so that it appears doubtful whether, after all, the hydrogen dioxide itself and not the fluid containing it has been the cause of the symptoms in the case just alluded to. On the other hand, probability is lent to the theory that the symptoms above spoken of are due to emboli by the statements of Colasanti and Brugnola, that hypodermic injections of the dioxide rapidly kill the rabbit by causing general gaseous oxygen-emboli; that in the dog they produce a local emphysema, followed by convulsions, urobilinuria, and other disturbances.

**BENZOYL-ACETYL-PEROXIDE.** — *Benzozone.* — *Acetozone.* — The pure peroxide occurs in a white crystalline mass, slightly soluble in alcohol; prone to undergo decomposition spontaneously, and capable when heated in a confined space, or when powdered or ground, of exploding. It is slowly dissolved and decomposed by water, and in contact with alkaloids and organic matters of all kinds it undergoes rapid change with oxidation of the decomposition substances.

Acetozone is the benzoyl-acetyl-peroxide diluted with a neutral drying powder, so that it contains fifty per cent. of the pure drug. Fifteen grains of the pure drug, or thirty grains of the commercial drug, may be dissolved in one and a half gallons of water, thus forming an active solution which must, however, be used within thirty-six hours after making. Benzoyl-acetyl-peroxide is an active germicide; experiments in the laboratories of the United States Government in the Philippines show that one part of the hydrolized substance to 177 of water, containing only 0.05 per cent. of active oxygen, destroys all germs, including spores, almost instantly, and even at a dilution of 1:3000 vegetating germs, as a rule, are killed within one minute, but the spores require a longer time. On comparing these results with similar ones with hydrogen peroxide, 1:1000, and phenol 5 per cent., it was shown that hydrogen peroxide, although it contained ten times as much active oxygen as the solution of benzoyl-acetyl-peroxide, was by no means as effective, and the same may be said of phenol. It was further shown that one part in a thousand absolutely destroys, and that one to thirty thousand distinctly inhibits, the growth of the comma bacilli. In the experiments of the discovery of acetozone (Feer and Novy), one drachm of it a day given to a dog weighing eight kilos for weeks produced no sensible effect, and it is probable that it is not taken into the blood at all. Charles L. Bliss states that the peroxide is eliminated in the form of hippuric acid.

Benzoyl-acetyl-peroxide has been used in the United States Philippine hospitals as an intestinal germicide with most excellent results in *cholera*, given in double capsules in doses from 0.2–0.32 gramme (4–5 grains) every two to four hours. It was found that when the stomach was full at the time of administration vomiting frequently occurred, probably due to the decomposition of the peroxide by the organic matter present, since no irritation was produced when the stomach was empty. Benzoyl-acetyl-peroxide has been employed primarily by Wasdin, and subsequently by Harris and others in *typhoid fever*, with alleged most extraordinary results in the reduction of the local and general symptoms,—one hundred and thirty to two hundred and ten grains being administered in the twenty-four hours.

Acetozone has been used locally as a germicide with alleged excellent results in *gonorrhœa*, *malignant œdema*, *tinea tonsurans*, *infected ulcers*, and similar affections. In surgical cases the dry acetozone may be applied directly to the wound. When it is desired to especially affect the intestinal tract, the drug should be given in double capsules so as to insure as far as may be its entrance unchanged into the duodenum.

## V.—CARBON COMPOUNDS.

## PHENOL.

Phenol (Carbolic Acid, Phenyllic Alcohol, Hydroxybenzene) is a substance obtained from coal-tar by distilling at a temperature of between 300° and 400° F., adding to the distillate a hot concentrated solution of potassium hydroxide, and, after this, water, separating the light oily matters which rise to the top, and adding hydrochloric acid to the heavy alkaline bottom layer, when impure carbolic acid separates. This impure carbolic acid is of a dark color, and contains several congeneric bodies, especially xylic and cresylic acids. These acids are as active germicides as is phenol, so that crude carbolic acid is very largely used.

The official phenol should contain at least ninety-six per cent. of absolute phenol. It occurs at ordinary temperatures in minute, colorless, transparent plates, or long rhomboidal needles, often fused into a mass, having a hot, corrosive, peculiar taste and odor, resembling but decidedly different from those of creosote. When opportunity is afforded, solid carbolic acid absorbs water from the atmosphere and melts into an oily-looking, colorless liquid. It is inflammable, neutral to test-paper, but combines with bases; soluble in about twenty parts of water, very soluble in alcohol, acetic acid, ether, glycerin, and the volatile and fixed oils. Nitric acid converts it into picric acid.

**Official Preparations:**

Phenol [Carbolic Acid] .....	1 to 2 grains (0.06–0.13 Gm.).
Phenol Liquefactum (86.4 per cent.) .....	1 to 2 minims (0.06–0.13 Gm.).
Glyceritum Phenolis (16 per cent.) .....	5 to 10 minims (0.3–0.6 C.c.).
Unguentum Phenolis (3 per cent.) [Carbo-	
lated Vaseline] .....	External use.

**Physiological Action.**—*Local Action.*—In concentrated form carbolic acid is a mild escharotic, its momentary application to the sound skin producing burning pain and a white discoloration which changes to a reddish stain, gradually fading away as the skin desquamates. If the application be prolonged an eschar forms.

Carbolic acid in sufficient concentration is poisonous to all forms of protoplasm; thus, even its weak solution arrests the movements in ciliated cells and in white blood-corpuscles (T. M. Prudden, Labée). It appears, however, to act especially upon the central nervous system and upon the peripheral nerve-endings: as was simultaneously pointed out by Erasmus Wilson and J. H. Bill, it is a local anesthetic.

Phenol is one of the oldest and one of the most popular of all germicides, but its power and reliability are usually overestimated.

According to Van Erlingen, a five-per-cent. solution destroys the viability of anthrax spores after thirteen days' exposure. On the other hand, Koch has found that a three-per-cent. solution of phenol will destroy the anthrax spores in two days. According to Nocht, the activity of carbolic acid varies very greatly at



different temperatures. Thus at room temperature a five-per-cent. solution failed to destroy the anthrax spores after several days' exposure, but when kept at a temperature of 37.5° C. the same solution was sufficient in three hours. It is evident, however, that the common statement that five-per-cent. solution of phenol is equivalent to 1:1000 of corrosive sublimate is *not true*, since the 1:1000 solution of corrosive sublimate will destroy the viability of the anthrax spores in two or three minutes.

Of the less resistant germs, phenol is an efficient destroyer.

Thus, Burgess found that a 1:40 solution destroyed the bacillus coli communis in five minutes, corresponding to 1:2000 corrosive sublimate solution. In Sternberg's experiments 0.8 per cent. destroyed the pus cocci in two hours' exposure. Boer has determined that in the absence of spores 1:300 solution is efficient against the anthrax bacillus in two hours.

*Absorption and Elimination.*—Phenol is readily absorbed through the gastro-intestinal mucous membrane as well as through the skin. Hoppe-Seyler found it in the blood, where it probably circulates as an alkaline carbolate and also uncombined. It is rapidly eliminated, having been detected in the urine by Almén, by Patrouillard, by Salkowski, by Hoppe-Seyler, by Waldenström, and by Hauxmann: Hoppe-Seyler detected it in the saliva, and it probably occurs in all the secretions. The researches of Baumann, which have been substantially confirmed, show that the phenol is changed into phenol-sulphonic acid [ $C_6H_5O.SO_2.OH$ ], which finally unites with alkalis and is eliminated as a phenolsulphonate. Portions of it are also excreted as glycuronic acid, hydrochinone and other oxidation compounds. The black coloring matter of the characteristic urine of phenol-poisoning is in all probability an *educt from phenol*, formed by its partial oxidation. When large quantities are administered, some of it escapes unchanged.

In a fatal case of poisoning Patrouillard obtained an oily fluid, believed to be pure carbolic acid, by shaking the urine with ether, allowing the mixed fluids to separate, and removing the ethereal layer and evaporating.

Hauxmann has proved that this black coloring matter is not altered hematin or any fixed coloring principle, by finding that the urine is cleared up by heating after the addition of an acid; and his conclusion is corroborated by the observation of Stevenson, of Guy's Hospital, who determined that the black urine does not contain more than a normal proportion of iron. When carbolic acid is oxidized outside of the body, as by the action of potassium permanganate, oxalic acid is formed; and Salkowski has shown that when phenic acid is given to animals oxalic acid appears in the urine. Other observers have, however, failed to detect these oxalates. Fr. Schaffer, A. Uerbach, and E. Baumann and C. Preusse found that the phenol was at least in part oxidized into *hydrochinone* and partly into a greenish-black substance upon which the coloring of the urine seems to depend. The researches of L. Brieger led him to the conclusion that when phenol is taken in not too large quantities a portion of it unites with sulphuric acid and a portion of it is converted into various colored oxidation products, some of which are very poisonous. According to the experiments of W. Kochs, this change occurs in the large abdominal glandular viscera.

Schmiedeberg has come to the conclusion that no phenol is oxidized in the body, but that it is all eliminated in combination with sulphuric acid, or to

a less extent with glycuronic acid. Reale affirms that when the sulphuric acid has all been appropriated phosphoric acid is attacked by the phenol and a phospho-carbolate formed.

*Production of phenol in the Animal.*—Städeler discovered that when sulphuric acid was freely added to cow's urine the latter yielded upon distillation phenol, and concluded therefrom that normal urine contains carbolic acid. He has been corroborated by Buliginisky and by Hoppe-Seyler; so that phenol is certainly a constituent not only of the urine of cattle, but also of that of men, dogs, horses, and probably other animals. Baumann has succeeded in producing phenol out of fibrin by a protracted digestion with the pancreatic glandular substance, and Nencki and Brieger have found that it is constantly present in normal human feces. Its elimination by the urine is enormously increased in ileus (one-hundredfold, Salkowski), and diminished in anemia, phthisis, scorbutus, scrofula, and cancer (Brieger). It is quite possible that the phenol is formed in the intestine by fermentative changes, as Baumann has noticed the closely allied substance indol produced by the putrefactive changes in a mixture of albuminous substance with a small quantity of pancreas and a little ammonium carbonate. In this connection it is interesting to note that Christiani has not been able to find phenol in the urine of chickens fed upon vegetable diet, although a notable amount is present when a flesh diet is allowed. In a series of experiments I. Munk obtained three grammes as the average excretion of twenty-four hours from a horse.

*General Effects.*—The largest therapeutic doses of phenol produce no distinct symptoms. Reserving the details as to the effects of toxic doses for the section on toxicology, it is sufficient for our present purpose to state that the prominent symptoms induced by lethal doses are disturbance of respiration, stupor deepening into coma, rapid, feeble pulse, muscular weakness, abolished reflexes, collapse, fall of temperature, and albuminous or bloody urine, ending in death from central paralytic asphyxia. In some cases convulsions occur.

According to Isidor Neumann, to Ernest Labée, and to Salkowski, a poisonous dose of phenol causes in the frog a paralysis which usually affects first the hind legs,\* but eventually spreads to the front legs and involves all parts of the body. After a time there are developed tetanic convulsions, which are apparently reflex in their nature, and are said to be excited by external stimuli or irritations.

Upon mammals phenol acts in very much the same way as it does upon the batrachian. According to W. Kempster, in the mouse and rat it causes intense muscular weakness, followed by violent convulsions and stupor. In the rabbit (Neumann, Salkowski) phenylic alcohol produces muscular weakness, often accompanied by tremblings and restlessness, at last giving place to violent convulsions. As has been pointed out by Turtchaninow, the tremors first commence as peculiar tremulous contractions of isolated muscles, and then of muscle groups which are irregular, and not at all symmetrical. Early in the poisoning the respiration is affected; and death, which usually occurs in the midst of convulsions, is owing to a *paralysis of the respiration*, since in acute cases the heart is found beating continuously immediately after death. According to the researches of Jules Lemaire, in the dog symptoms very similar to those detailed above are caused by lethal doses of the drug; and Husemann states that in mammals and in birds the characteristic phenomena of phenol poisoning are clonic convulsions, sinking of the temperature, diminution of sensibility, dyspnoea, free salivation and secretion of tears, keratitis, and conjunctivitis. According to the latter authority, albuminuria and hematuria are occasional phenomena.

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\* According to Lemaire when a frog is allowed to swim in water impregnated with phenol, the front legs are first affected.

Phenol, being a universal poison, acts upon the whole system; so that the detailed study of its physiological effects when given internally is simply an endeavor to determine what tissues are most susceptible to its influence.

*Nervous System.*—The influence of phenol on the cerebrum is not very intense in the lower animals, but in the higher species, and especially in man, results in the early production of stupor.

The convulsions are not peripheral, since they do not occur in a limb whose connection with the spine has been severed by division of the nerve, and do take place in a leg which has been protected against the local action of the poison by tying the artery (Salkowski, Labée). They are, therefore, either cerebral or spinal. Although there is a distinct conflict of evidence, it seems established that the convulsions are of *spinal origin*. After large doses there is developed later a paralysis of the spinal motor centres.

Labée and J. R. Haynes failed to get them after section of the cord, but in the far more numerous experiments, upon frogs and mammals, of Salkowski, of Berb and Jogel, of J. S. Stone, and of T. Gies, convulsions occurred after destruction of the medulla, section of the cord, and other operative procedures separating the brain from the lower nervous system. The failures of the first-named experiments are explainable by the facts that the paralyzing influences of phenol are usually first manifested upon the hind legs, and that very large doses were employed.

In phenol-poisoning the nerves and muscles are not distinctly paralyzed (Salkowski, Hoppe-Seyler), but the very careful experiments of Gies have proved that the muscles are less sensitive and more easily exhausted than is normal.

*Circulation.*—The action of phenol upon the heart is not a very marked one, but there can be little doubt that in sufficient amount the drug depresses the heart and perhaps also the vaso-motor centres.

After death from acute poisoning the heart is usually found to be beating regularly (Salkowski), but in some cases of slow poisoning the death has seemed to be ultimately caused by cardiac diastolic arrest. In Hoppe-Seyler's manometrical studies the arterial pressure was not affected until convulsions came on, when it rose from the effects of the general muscular contraction. It afterwards fell very decidedly and permanently.

Reduction of the arterial pressure has been shown by Gies to be the characteristic effect of the phenol: in his experiments moderate doses of phenol failed to affect the pressure after section of the cord, while in the normal animal neither asphyxia nor stimulation of a sensitive nerve elevated the lowered pressure, although the heart was beating forcibly—facts that demonstrate that phenol paralyzes the vaso-motor centre in the medulla before it markedly affects the heart.

*Respiration.*—According to Salkowski, Labée, and other authorities, in the first stages of phenol-poisoning the respiration is remarkably increased in frequency. This acceleration Salkowski believes to be due partly to a stimulant action upon the peripheral vagi and partly to a similar influence upon the respiratory centres. The final paralysis of respiration by phenol is almost certainly due to a direct action upon the respiratory centres.

Salkowski states that the respirations are very shallow, and that the diaphragm scarcely participates at all in them, but that if the cervical vagi be cut they become



much slower, deep, and regular. On the other hand, if phenol be given to an animal suffering from section of the pneumogastrics, the slow breathing is very much accelerated. From the former of these facts the German investigator draws the conclusion that the accelerated breathing produced by phenylic alcohol is in part due to a stimulation of the peripheral vagi, and from the latter fact that it partly arises from a similar action upon the respiratory centres.

*Temperature.*—According to the researches of Hobart A. Hare, phenol injected into rabbits produces a very distinct fall in the bodily temperature, which is usually, but not always, coincident with the lowering of the arterial pressure. In the calorimetric studies made by Hare the action upon heat-production and heat-dissipation in the normal animal appeared to be various, sometimes production and sometimes dissipation being alone affected, while in other cases both functions were altered. Some years ago Emil Erls found that in mild putrid poisoning in animals phenol diminished greatly the fever-heat; when the poisoning was more severe it had no influence. The calorimetric studies made by Hare upon fevered animals were fairly constant in their results, although the method of experimentation was not satisfactory, because the drug was given to the fevered animals at a time when it was uncertain what would have been the production of heat without its influences. Nevertheless, the experiments indicate that phenol may affect the thermogenetic functions of the body in two ways: first, by diminishing the production of heat; second, by increasing the dissipation of heat.

*Therapeutics.*—In the doses in which it is usually given, phenol exerts no perceptible effect upon the system. It has been used to a considerable extent in zymotic diseases for the purpose of destroying the germs in the blood, but is of no value for such purpose. There is no reason for believing that micrococci or bacteria are more sensitive to its action than is the human organism; and clinical experience in zymotic diseases has certainly demonstrated the uselessness of the drug.

The use of phenol in *tetanus*, as originally proposed by Baccelli, has in a number of cases been attended by apparently beneficial results. Ascoli has collected thirty-four cases with only one death.

Exactly how phenol acts has not been determined; Heddaeus believes that it neutralizes the toxin in the same manner as does the antitoxin. It is to be given hypodermically in the form of two-per-cent. solution, from five to fifteen grains (0.3–1 Gm.) in the twenty-four hours. (See H. C. Wood, Jr.) Courmont and Doyon in a research upon mice, guinea-pigs, and rabbits found that in these animals carbolic acid is useless against tetanus infection.

For its local effects, phenol is a very valuable remedy in the treatment of various forms of nervous irritability of the gastro-intestinal mucous membranes, especially when there is also a tendency to fermentative changes in the food, as the result of imperfect digestion. In *nervous vomiting*, and in *gastrodynia*, it may be given in doses of from one to two grains, repeated at intervals varying from fifteen minutes to two hours, according to the symptoms of the case. In

*diarrhœa* of irritation, as well as of *relaxation*, it is often of the greatest service. The combination of one or two grains of phenol with ten to twenty grains of bismuth subcarbonate, given in emulsion or in capsules, is one of the most generally useful of diarrhœa mixtures.\* In *gangrene of the lungs* the internal administration of carbolic acid combined with the use of a weak solution, ten grains to the fluidounce, by atomization, is said to be of great service. The use of carbolic acid as an antipyretic, as inaugurated by H. M. Desplats, has not found favor, and is scarcely justifiable.

The external use of phenol belongs to the domain of surgery rather than of medicine, and we shall discuss it very briefly. As a *caustic*, phenol is not available when large masses of tissue are to be destroyed, but it may often be employed with advantage against *condylomata* and similar growths. Even in such cases, to be efficient, it must be in the most concentrated form. In *diphtheria*, *ulcerated sore throat*, and *aphthous stomatitis* its concentrated solution in glycerin may carefully be applied, by means of a camel's-hair brush or a mop, as a mild caustic scarcely capable of destroying sound tissue. In various forms of *indolent ulcer* and in *ill-conditioned wounds* phenol affords a very useful stimulant application; in *burns*, properly diluted with oil (ten grains to one fluidounce), it is one of the very best remedies that can be used, relieving pain by its anesthetic properties and at the same time lessening suppuration and facilitating cicatrization.

The use of phenol as a local anesthetic has been entirely done away with by the discovery of the powers of cocaine.

So far as we know, the first to suggest and employ *deep injections* of carbolic acid as a means of combating *deep-seated inflammations* was J. A. Eames; but the method has been especially studied and practised by Hueter with asserted extraordinary success in *glandular swellings and inflammations*, *phlegmons* of all grades and characters, *erysipelas*, *poisoned wounds*, *inflamed bursæ*, *hydrocele*, and even in *bone disease*.

The practice has been followed with satisfaction by Aufrecht in *erysipelas*, by Senator, Mader, and Kunze in acute and subacute *rheumatism*, by Hagen in several diverse inflammations, and by I. Schmidt in chronic *synovitis*. These injections have been practised by Hagen with asserted excellent results in severe *angina* (the injections were in the neighborhood of the second tracheal cartilage): by Moses K. Taylor in one hundred and fifty cases of *buboes* and other enlarged glands, with uniform success: by Mutschler with success in *anthrax*. The total evidence seems to show that this method of treatment is both safe and effective.†

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\* In dispensing this, if capsules be used, the two ingredients should be thoroughly mixed before putting in; if an emulsion be employed, the bottle should be stood on its cork or laid upon its side, to prevent permanent separation of the bismuth.

† As this method is of surgical rather than medical interest the reader is referred for details either to the authors quoted, or to surgical treatises.

**Toxicology.**—Probably on account of the ease with which it is procured and the quickness of its action, phenol is among the most popular of poisons. According to Harris, out of five hundred and forty-nine fatal cases of poisoning with it which occurred in England during four years four hundred and twenty were suicidal.

The symptoms usually appear in a very short time after the ingestion of the poison, and when the dose has been sufficient may develop so rapidly that death occurs within three minutes. Usually the patient lives from one to ten hours, and life has been protracted for sixty hours.\*

Taylor records a case in which about an ounce is supposed to have been ingested, and in which the man fell in a stupor within ten seconds after taking the fatal draught, two minutes afterwards was totally unconscious, pulseless, with irregular distant gasping respirations, and in less than a minute later was dead, apparently from cardiac paralysis, since the impulse of the heart was entirely lost before the cessation of respiration.

Usually, but not always, a burning pain is first felt in the mouth, œsophagus, and stomach, followed in a few minutes by nausea, cold sweats, and stupor deepening rapidly into insensibility and collapse. During the period of insensibility, complete abolition of reflex movements and anesthesia of the mucous membranes have sometimes been noted: † indeed, it is scarcely doubtful that in all cases both sensibility and reflex movements are profoundly affected. Convulsions are only exceptionally present. The symptoms of collapse are usually well developed, and the pulse is generally feeble and very frequent, but has been recorded as being reduced to from 40 to 50 per minute (Hainworth). Hemoglobinuria has been noted. Dyspnoea is often extreme; the respirations may be stertorous, are usually very rapid, and, in the advanced stages, shallow. In very rapid cases they are irregular and suspended at intervals. Total temporary amaurosis, with contraction of the pupil, has been noted.‡

In some cases of carbolic acid poisoning a great amendment has occurred and consciousness been restored, but after some hours rather sudden fatal collapse has come on. The minimum fatal dose of carbolic acid is not known; but half an ounce has several times caused death,§ and a little over a drachm is reported to have killed a man sixty-four years old (Swain); in a case of puerperal metro-peritonitis fifty drops contributed towards the fatal result (A. D. L. Napier).

The free external use of phenol is by no means devoid of danger; Falckson, after two hours' exposure to phenol spray, recovered from his urine thirty grains of phenol, and he describes a marasmus or chronic poisoning resulting from the surgical use of the remedy.

\* Case, *Sydenham Soc. Year-Book*, 1871-72, 446; amount taken, one and a half ounces of the commercial acid.

† Case, *Journ. de Pharm. et de Chim.*, Dec. 1871.

‡ Case, *Berlin. Klin. Wochenschr.*, xix. 748.

§ *Med. Times and Gazette*, 1870, ii. 474; *Phila. Med. and Surg. Rep.*, Jan. 1870; *Lancet*, 1878, ii. 510.



The symptoms are said to be headache, loss of appetite, bronchial irritation, which finally may become very severe, severe pains in the region of the kidney, recurring vomiting, pruritus, or various paresthesiæ, and loss of power in the legs. (See also Wallace.)

A single vaginal injection has produced very severe constitutional results. R. Köhler reports the case of two journeymen joiners, suffering from scabies, who applied externally each about a half-ounce of phenol, in watery solution. One of them was found dead. His fellow, who suffered from unconsciousness and drunken delirium ending in unquiet sleep, after his recovery stated that directly after rubbing himself with the solution he had giddiness, that seven or eight minutes later his companion complained of burning, but that of what took place after this he knew nothing.\*

It is scarcely necessary to refer in detail to cases in which serious results have followed the surgical use of phenol.† A very severe case of poisoning is recorded, in an infant, produced by the use of carbolized cotton wool. The local application of phenol has in a number of instances been followed by local gangrene, which A. Frankenburg has attributed to thrombosis, but Harrington believes has been due to a direct chemical action.

The *post-mortem* lesions of phenol-poisoning are usually well marked. If the acid has been ingested in a concentrated form, white, hardened spots are found upon the mucous membrane of the mouth, œsophagus, stomach, and even intestines. They are, of course, due to the local action of the poison, and are sometimes blackish in the centre, or even blackish throughout, and very generally are surrounded by a red inflammatory zone. The liver, spleen, kidneys, and indeed all the organs, are found filled with dark, imperfectly coagulated blood, such as is habitually found after death from asphyxia. Neumann found in experimental poisoning in the lower animals constantly fatty degenerations, but Salkowski was unable to obtain such changes and, according to Husemann, the fatty degeneration of the liver and kidneys is neither in man nor in animals a constant characteristic phenomenon of phenol-poisoning. Reuder found the renal epithelium degenerated in a man who had been fatally poisoned by the drug.

The *diagnosis* of phenol-poisoning during life ought in most cases to be practicable; for, although the symptoms simulate some forms of apoplexy too closely for the diagnosis to be made from them, very generally the odor of the drug can be perceived about the person of the victim, and close examination of the mouth will nearly always reveal traces of the local action of the phenol, in the form of *white, hardened, or corrugated* patches of mucous membrane. Either these or a *blackish urine* in conjunction with the symptoms are diagnostic. After death a strong odor of phenol can almost always be perceived when the body is opened, and the mucous membrane of the stomach

\* For other fatal cases consult *Bull. Thérap.*, lxxv. 285.

† Consult *British Medical Journal*, March 1, 1873,—death from absorption by a wound four inches long; *New York Medical Gazette*, April, 1871; *British Medical Journal*, 1868, 220,—two fatal cases; *Med. Times and Gaz.*, 1878, ii. 461; *Wiener Med. Wochenschrift*, 1879, xxix. 1233.

affords very reliable evidence as to the cause of death. According to A. Hiller, the urine of phenol-poisoning as first passed varies from a clear yellow to a golden yellow, and upon standing in the air becomes dark olive and finally often blackish-green. Sometimes it is grass-green, but it may appear to be normal. This phenol urine, if treated with nitric acid and afterwards with potassium hydroxide, becomes, after a certain degree of concentration, blood-red or brown-red, changing through pea-green to violet. Phenol mixed with urine does not answer this test. The absence of phenol urine proves that the case is not one of poisoning. Baumann and Hueter declare that the earliest symptom of the poisoning is the disappearance of the sulphates from the urine.

In the *treatment* of a case of phenol-poisoning emetics are generally useless, owing to the existing paralysis of the stomach, and the stomach-pump must be employed to empty the viscus. As antidotes to phenol various substances have been suggested, but are of doubtful value. Those which have attracted most attention are the sulphates and alcohol. It is very doubtful if the sulphates have any antidotal action but as they are at least harmless they should be employed. Alcohol is in no sense antidotal to phenol. In external burns it acts favorably because being a good solvent for phenol it washes the irritant away (Ascher and Clarke and Brown); in internal poisoning it may easily do harm by aiding absorption of the poison. It may, however, be useful to wash out the stomach providing no residue is left behind.

The practical treatment of phenol-poisoning should be lavage of the stomach with ten-per-cent. solution of alcohol (or whisky), followed by administration of magnesium sulphate, the use of stimulants as indicated and the treatment of the subsequent gastritis with demulcent remedies.

Alkalies in excess have been specially commended by Husemann, who employs saccharated lime.\* In 1878 Baumann and Hueter stated that if a dilute sulphuric acid or a soluble sulphate be given freely to the animal poisoned with carbolic acid the latter will be converted into a harmless phenol-sulphonic acid.†

David Cerna and also Cafawy believed to have obtained favorable results in experimental poisoning. Their technique was called in question, however, by Tauber, who found in a number of experiments that neither the sodium sulphate nor the pyrosulphate evinced any antidotal influence in the poisoned rabbits. He further concluded, as the result of his experiments, that the sodium sulphite is of distinctly antidotal value. Sollmann and Brown likewise were unable to demonstrate any antidotal action of sodium sulphate.

On the other hand, Jos. Szydlowsky saved a pulseless and apparently dying child, ten hours after the ingestion of phenol, by hypodermic injections of ether and the administration of dilute sulphuric acid and sodium sulphate. In a careful

\* Dissolve sixteen parts of sugar in forty parts of distilled water, and add five parts of caustic lime; digest for three days, stirring from time to time, filter, and evaporate to dryness. The product thus obtained dissolves easily in water.

† For a study of sulphocarbolic acid, see *La Tribune Méd.*, July, 1884, 328. M. F. Vigier affirms that, while not poisonous to the higher animals, it is an active antiferment. M. Rabuteau (*Compt.-Rend. Soc. Biol.*, 1882 iii. 42) finds that the acid is simply a feeble purgative.

study free from the objections urged against some of the earlier investigators Pio Marfori concluded that the soluble sulphates, given either through the gastro-intestinal canal or injected hypodermically, are distinctly antidotal to carbolic acid, but that there is a limitation to their power, so that if too much phenol has been taken the sulphates will prove of no value.

Maberly has recently suggested iodine as a chemical antidote to phenol.

**PHENYL SALICYLATE.**—*Salol*.—This is a white, nearly tasteless, insoluble crystalline powder, which is prepared by replacing one atom of the hydrogen of salicylic acid by phenol. It is decomposed by alkalis, and, consequently, is broken up in the intestinal tract, yielding about thirty-six per cent. of phenol, and sixty-four per cent. of salicylic acid. Although less powerful as a poison than are its united ingredients, probably because it is broken up slowly in the intestines and escapes with the feces to some extent unchanged, salol is capable of producing concurrent symptoms of salicylic-acid and of phenol-poisoning. Kumagawa has found that it increases nitrogenous elimination.

Salol was originally introduced into medicine by Sahli as an antirheumatic, but is at present employed solely as an intestinal disinfectant. According to Lesnik it has practically no influence upon ordinary bacteria. Its effectiveness as an intestinal antiseptic evidently depends upon phenol and salicylic acid, which are liberated by its decomposition. In the experiments of Kumagawa on animals, large doses of salol failed to lessen the elimination of indican by the urine or the number of bacteria in the intestines; nevertheless, in *typhoid fever*, *intestinal indigestion*, and allied complaints, salol may be considered as probably the most effective of our intestinal antiseptics.

Externally salol has been used as an antiseptic dressing, but is of very little value.

One hundred grains a day of salol have frequently been given without serious effect, probably because the larger proportion of the salol has escaped unchanged with the feces. Hesselbach claims that the long-continued use of salol is dangerous when the kidneys are diseased, on account of the irritating influence of phenol on these organs. The ordinary dose is from ten to fifteen grains (0.6–1 Gm.), as an intestinal disinfectant, administered in capsules one hour after meals.

**PHENOL-SULPHONIC ACID.**—Both the sodium and zinc salts of *sulpho-carbolic acid* are official in the U. S. Pharmacopœia. (Sodii Phenolsulphonas, Zinci Phenolsulphonas.) The sulphocarbolates were introduced some years ago as intestinal antiseptics, for which purpose it was evidently expected they would possess the antiseptic virtues of carbolic acid and the innocuousness of the sulphocarbolates. It has been shown, however, by Withers that they are not possessed of any direct antiseptic power. More recently it has been claimed for them that they are decomposed in the intestinal tract with the liberation of carbolic acid, but we know of no experimental or scientific evidence tending to show the truth of this belief, and their value is extremely doubtful.



## CREOSOTE.

This substance is defined by the U. S. Pharmacopœia to be a mixture of phenols, chiefly guaiacol and creosol, obtained during the distillation of wood-tar, preferably of that derived from the beech (*Fagus sylvatica* Linné). It is stated that the beech-wood creosote ranges in the amount of guaiacol from sixty to ninety per cent. It has been much confused with phenol, and for many years most of the creosote of the drug-stores was an impure carbolic acid. For the tests distinguishing creosote from carbolic acid, see United States Dispensatory. The creosote of commerce is an oleaginous liquid, colorless, or brownish or reddish, having a caustic taste and a penetrating disagreeable odor, which while resembling that of phenol markedly differs from it in being more smoky. It requires 140 times its weight of water to dissolve it but is freely soluble in alcohol.

*Creosote Carbonate* or *Creosotal* is a mixture of the phenol-carbonates of the several constituents of creosote, containing about ninety per cent. of creosote. It is a thick, oleaginous, pale yellow, almost tasteless liquid, insoluble in water, soluble in fatty substances. Although unofficial it has been largely employed.

**Official Preparations:**

Creosotum.....	5 to 15 minims (0.3-1 C.c.).
Aqua Creosoti (1 per cent.).....	$\frac{1}{2}$ to 1 fluidrachm (2-4 C.c.).

**Physiological Action.**—The physiological effects of creosote have never been carefully and thoroughly studied. It certainly rivals phenol in its antiseptic power.

Sternberg has found that a 1:200 solution of creosote destroyed the pus cocci in two hours' exposure. Bucholz ranks creosote as superior to phenol, but inferior to salicylic acid.

Creosote is, when applied locally, a paralyzant to the nerves, and probably to all higher tissues; indeed, it has been generally believed to be physiologically almost identical with carbolic acid. It differs, however, greatly from carbolic acid in its toxicity and in its therapeutic usefulness.

The symptoms of creosote-poisoning are similar to those caused by phenol,—namely, burning in the gullet and stomach, vertigo, faintness, unconsciousness, collapse, blackish urine, stertorous breathing, and great cardiac depression. Zawadzki reports a death alleged to have been produced by three six-drop doses of creosote, taken in the twenty-four hours.

Freudenthal\* reports the case of a woman who took six hundred drops of creosote in a very short time, the ingestion being followed almost immediately by unconsciousness, with intense trismus, contracted, immobile pupils, and general

\* For other cases of creosote-poisoning, see Müller (*Würtemb. Correspondenz-Blatt*, 1869), T. Stevenson (*Guy's Hosp. Rep.*, 1875, xx, 144), Pürckhauer (*Friedreich's Blätter f. Gericht. Med.*, 1883, 430), F. Grinell (*Med. News*, xl, 345), Manouvriez (*Soc. Méd.-Légale de France*, vii, 108), and Faisans (*Bull. Méd. Soc. Méd. d'Hôp. de Paris*, 1896).

cyanosis, but in which recovery occurred without the administration of remedies. He further states that subsequently the same patient, by increasing the dose of creosote, was able to take five hundred drops daily without ill effect.

The *absorption and elimination* of creosote are very rapid.

Saillet, within the nine hours following the administration of eight centigrammes, obtained from the urine forty-eight milligrammes; after sixteen centigrammes, one hundred and eleven milligrammes; and it would appear that about two-thirds of the dose escapes from the body through the kidneys in the time mentioned. Imbert recovered one gramme of guaiacol from the urine after the hypodermic injection of two grammes; after two grammes of a mixture of guaiacol and creosote, sixty centigrammes; and so on: so that it would appear that a portion of the creosote is destroyed in the body. This conclusion is, however, rendered doubtful by the fact that the creosote escapes through other channels than the kidneys.

Creosote has been found abundant in the sputa of phthisical patients, and, indeed, Catillon affirms that it is chiefly thrown off through the lungs. It occurs in the urine probably in part as oxidized educts, but chiefly as creosol and guaiacol sulphates: so that, as shown by Hobert A. Hare, sulphuric acid and the soluble sulphates are antidotal to it.\*

**Therapeutics.**—The most important use of creosote is as a stimulant expectorant in *chronic bronchitis* and *phthisis*. The old theory that creosote did good in phthisis by virtue of its antiseptic action is, in the light of recent research, hardly tenable.

Any such action must be purely local,—i.e., due to creosote excreted in the lung,—since F. Hölcher and Richard Seifert found that in young rabbits and dogs to which guaiacol has been freely given the serum of the blood was at no time capable of checking the development of bacilli in agar-agar. Schill and Fischer (quoted by Sternberg) found that a one-per-cent. solution of creosote failed to destroy the tubercle bacilli in the sputum after two hour's exposure. It seems to be established that creosote is largely eliminated with the sputa; but Bogdonovitch and other clinicians or experimenters have found the bacilli abundant and active in the sputa of phthisical persons taking the remedy. Brissonet, Hölcher and Seifert present evidence to show that guaiacol neutralizes in the blood those poisonous products of bacillary growth which are the cause of the fever, sweating, disordered digestion, etc., of the phthisical patients; in other words, that creosote acts chemically in the blood. At present this seems to be nothing more than an ingenious theory.

On account of its local action as a nerve paralyzant, creosote is frequently employed with great advantage in *nausea*, *vomiting*, or *diarrhœa* dependent upon excessive irritability, without acute inflammation of the gastric or intestinal mucous membrane; it has thus been successfully used in the *vomiting of pregnancy* or of *hysteria*, in *cholera morbus*, *cholera infantum*, *lienteric diarrhœa*, *typhoid fever*,

\* Imbert finds that the proportion of creosote eliminated diminishes with the increase of the dose. Thus, after an enema of one gramme, fifty-four to sixty per cent. was found in the urine; after two grammes, forty-eight per cent.; after four grammes, thirty per cent. When four grammes were administered, the expectorations showed its presence for twelve hours. After a subcutaneous injection, Imbert was not able to recover from the excretions more of the creosote than after it had been given by enema. Although there were severe persistent pain and swelling, no suppuration or sloughing ever followed these injections. Imbert also found that the elimination ceased at the end of twelve hours after large as well as small doses (*Bull. Gén. Thérap.*, 1892, cxxii.). For methods of finding creosote in the urine, see also *Bull. Gén. Thérap.*, May 1892.

and even in *dysentery*. When in these cases there is a tendency to fermentation of the contents of the stomach or bowels, creosote is especially valuable, and may often be combined advantageously with an alkali or chalk. Whether it is in these affections superior to phenol is doubtful.

Externally, creosote has been employed for exactly the same purposes as has phenol. The skin diseases to the treatment of which creosote has been supposed to be best suited are those of a scaly character. In *burns* its efficacy has been insisted on, especially when there is excess of suppuration or of fungous granulations. Also in *chilblains* it is stated to be a useful application. Mixed with four parts of lard, it is said to have proved very serviceable in *erysipelas*. When applied to wounds it acts as a hemostatic, stopping the capillary hemorrhage, but it possesses no power to arrest the bleeding from large vessels. Accordingly, creosote-water has been applied locally in *menorrhagia*, and to arrest *uterine hemorrhage* and the bleeding from leech-bites. Wherever there are *foul ulcers*, gangrenous surfaces, or inflamed serous, mucous, or glandular tissues giving rise to fetid discharges creosote may be substituted for phenol; as examples may be mentioned fetid *leucorrhœa*, puerperal *metritis*, fetid *otorrhœa*, putrid or *diphtheritic sore throat*, chronic *empyema*, and chronic *fistula*. The strength of the application may vary from that of pure creosote to a one-per-cent. solution.

The ordinary dose of creosote is from three to five minims (0.2–0.3 C.c.) three to six times a day, in chronic cases increased to one or even two fluidrachms a day, as borne by the patient. Creosote in capsules should be taken upon a full stomach. Large doses of it should always be freely diluted with water and glycerin, or milk or cod-liver or other oils, to avoid local irritation. The hypodermic use of creosote, as practised by Perom in phthisis (ten-per-cent. solution in oil of sweet almonds), is not to be favored.

Creosote carbonate is claimed to have the advantages of being less disagreeable to the taste and better tolerated by the digestive apparatus. It is decomposed in the system, and is capable of producing blackish urine. It is, however, much less poisonous than is creosote, and probably when large doses are exhibited escapes in part from the alimentary canal. Fifteen drachms of it are asserted to have been given in a day without unpleasant symptoms; and it has been used hypodermically after warming, so as to increase its fluidity. It may be given in capsules, or preferably in emulsion in milk.

**GUAIACOL.**—*Methyl Pyrocatechin*.—Guaiacol is a phenoloid body, constituting from sixty to ninety per cent. of creosote, from which it may be obtained by fractional distillation, or it may be prepared synthetically. It occurs as a colorless crystalline solid, and also as a syrupy liquid of an agreeable aromatic odor. It is soluble in fifty-three parts of water and very freely in alcohol and ether.



*Guaiacol Carbonate* (*Duotal*) occurs as a neutral, white, almost tasteless and odorless crystalline powder, insoluble in water, soluble in forty-eight parts of alcohol.

#### Official Preparations:

Guaiacol.....	5 to 10 minims (0.3-0.6 C.c.).
Guaiacolis Carbonas.....	10 to 20 grains (0.6-1.2 Gm.).

Guaiacol acts in concentrated form as an irritant and as a germicide. As originally pointed out by André, it has also distinct anesthetic properties which are not, however, sufficiently pronounced to make the drug useful as a local anesthetic. In the experiments of J. Kuprianow guaiacol was found to be distinctly inferior to creosote and to phenol in general germicidal influence, but to be especially poisonous to the tubercle bacillus.

Guaiacol is absorbed and eliminated with great rapidity. Linossier and Lannois were able to recognize it in urine passed fifteen minutes after its local application to the skin, and to obtain from the urine of the next twenty-four hours nearly half of the whole amount used. In the experiments of Eschle the greatest part of the ingested guaiacol or guaiacol carbonate was eliminated within twenty-four hours, about half of it going out with the urine in combination with sulphuric acid; of the remainder the greater part was eliminated as glycuronic acid.

The general physiological action of guaiacol has not been studied to any extent, but appears to be similar to but less powerful than that of phenol.

**Therapeutics.**—The suggestion of Guinard that guaiacol be used externally as an antipyretic in phthisis has led to its trial in *pneumonia*, *typhoid fever*, and other acute diseases. The thoroughly cleansed skin of the abdomen or chest is painted by means of a camel's-hair brush with from twenty to fifty minims, and an impermeable dressing applied to prevent evaporation. The fall of temperature produced by the guaiacol used in the manner described follows with great certainty, but has too often been excessive and accompanied by pronounced collapse to allow the drug to be considered a practical antipyretic.

Guaiacol is used as a substitute for creosote in *tubercular* and other chronic *catarrhs*, and is very effective. It is also used locally in *lupus* and other forms of surgical tuberculosis. Thus, in *tuberculosis* of the *bladder*, and even in *chronic cystitis*, from fifteen to thirty minims of a five- to twenty-per-cent. solution in sterilized olive oil may be injected daily into the bladder. Inhalations of the aqueous solution (1:600) have been considerably used in *pulmonic tuberculosis*, but it is not probable they have any effect except upon the catarrh of the mucous membranes.

Guaiacol carbonate is much used as a substitute for guaiacol on account of its freedom from taste and of its being less irritant. It is, however, much less active than is guaiacol, both as a local and general

agent. In the experiments of W. Hesse it was found to be so slightly poisonous that it seems probable that when it is taken internally much of it passes through the alimentary canal unabsorbed.

ORTHOGUAIACOL-SULPHONIC ACID, or *Theocol*, occurs as a white, micro-crystalline, odorless, permanent powder, of a faint bitter saline taste, soluble in water and dilute alcohol. It has a powerful reducing action on silver salts and ferric compounds, and at once decolorizes permanganate solution. Hatch claims it to be of great value in *bronchitis*, *pneumonia*, *phthisis*, and all forms of infective inflammations of the lungs. He thinks it attacks the bacilli.

### CRESOL.

Homologous with phenol are the three isomeric compounds, orthocresol, metacresol, and paracresol, a mixture of which is recognized by the U. S. Pharmacopœia under the name of *cresol*. This is a colorless or straw-colored refractive liquid with a phenol-like odor, soluble in sixty parts of water and miscible in all proportions with alcohol and glycerin. It is a later product of the fractional distillation of coal-tar, and is practically the substance which has long been known in commerce as *cresylol*, or *cresylic Acid*.

Cresol is soluble in sixty parts of water at 25° C., but is rendered more soluble by the presence of soap. This is the explanation of the complete miscibility with water of the official compound solution of cresol, as well as the various proprietary preparations of cresol. The addition of lime salts and the use of hard water in making solutions of compound solution of cresol, on account of the insolubility of the lime soaps, produces a turbidity of the solution, which, however, it is claimed does not interfere with its germicidal activity.

#### Official Preparations:

Cresol. .... 1 to 2 minims (0.06-0.12 C.c.).  
Liquor Cresolis Compositus (50 per cent.) . . External use.

Although it seems established that cresol is a more active germicide than phenol, what knowledge we have of its physiological activities is derived so largely from studies of proprietary preparations, whose real combination is a matter of doubt, and is so imperfect that positive conclusions as to its exact value must be drawn with caution especially as the three cresols differ somewhat in their properties.

Henri Delplanque affirms that cresol is stronger than phenol as a germicide and has only one-fourth of its toxicity. Fränkel found that a 0.3 per-cent. solution of cresol destroyed the staphylococcus aureus, and the streptococcus erysipelatus in five minutes, while a two-per-cent. solution of phenol required fifteen minutes to accomplish the same result. The statement of Fränkel that the compound of cresol with sulphuric acid is soluble in water, scarcely irritant, and more powerful as a disinfectant than is phenol, seems to us highly improbable. Weiss found that a three-fourths-per-cent. solution of lysol \* destroyed various bacteria (*pus cocci*, *typhoid bacillus*, etc.) in five minutes, and the anthrax spores in one hour. According to the results of Burgess, however, lysol is not greatly superior to phenol.

\* Lysol appears to correspond closely in composition and strength to the official compound solution of cresol.

That cresol is poisonous has been proven by Faust, and Fries has collected thirty-eight cases of lysol-poisoning, of which eleven were from external use, with four deaths; twenty-seven from internal use with thirteen deaths. He places the toxic dose at about 4-5 C.c. for children, and 10-12 C.c. for adults. Blumenthal states that about 100 cases of lysol-poisoning occur annually in Berlin. Maass affirms that lysol is eight times less poisonous than is phenol, and one-half as poisonous as creolin. Tollens has shown that although paracresol is slightly less toxic than phenol commercial cresol is fully as poisonous if not more so than phenol, whether in aqueous or saponaceous solution. It is certainly less caustic in concentrated solution than is phenol.

The symptoms of cresol-poisoning are nausea and vomiting, general depression with stupor, fall of the bodily temperature, smoky, albuminous urine, ending in fatal cases in coma and collapse.

The compound solution of cresol offers a valuable substitute for phenol as a germicide in all purposes in which the older preparation is useful. It has the advantages of greater power, less irritation, and lower toxicity. Its saponaceous character makes it especially valuable in cleansing the skin or the surgeon's hands. Although its extremely unpleasant taste and odor lessens its value in intestinal *putrefaction* and *diarrhæas*, cresol has been recommended by Maass and Vondergoldz.

CREOLIN is a soluble preparation, containing, according to Pfreuger, 2.7 per cent. of phenols, mostly cresol, suspended by means of resin soap. It has been asserted that creolin is not poisonous, Jessner stating that he had given one hundred and twenty grains (7.77 Gm.) to a man without production of distinct symptoms. It is almost certain, however, that its apparent lack of toxicity depends upon its non-absorption, due to insolubility; and human poisoning has been caused by it.

Bitter has seen restlessness, anxiety, nausea, amblyopia, and a tendency to syncope, with a peculiar strong taste of tea or smoke, produced by the drug. The urine in some of his cases was dark and highly albuminous, acute nephritis having evidently set in. Fliesburg details a case of a three-weeks'-old babe who was killed by thirty drops of undiluted creolin, the chief symptom being those of violent irritation of the mouth and upper respiratory and digestive tracts. Death occurred chiefly through inflammation of the glottis.

Eisenberg asserts that a three-per-cent. solution of creolin will kill anthrax spores in forty-eight hours, but on the other hand both Esmark and Van Ermenegen failed to kill the anthrax spores with a ten-per-cent. solution after exposure for thirteen days. According to Burgess, a twenty-per-cent. solution of creolin destroyed the bacillus coli communis in five minutes, being equivalent to 2.5-per-cent. solution of phenol.

### NAPHTHALENE.

Naphthalene (*Naphtalin*) is a hydrocarbon obtained by the fractional distillation of coal-tar, or sometimes by the dry distillation of organic bodies. It is a white, shining, crystalline substance, fusible at 176° F., insoluble in water, but soluble in alcohol, chloroform, and ether. It is poisonous to the lower forms of life, and under the name of *tar camphor* has largely supplanted true camphor as a means of preventing the deposition by moths of eggs in woollen clothing, and the destruction by insects in natural history museums, etc. In internal medicine it was some years ago brought forward



by Dupasquier as an expectorant especially valuable in *chronic bronchitis* with a large amount of secretion. It has also been used with asserted excellent results as a *teniacide*, and as a vermifuge in cases of *seat-worms*, when it should be given by injection, from fifteen grains to half a drachm in two or three ounces of olive oil. First employed by Rossbach, of Jena, in *intestinal catarrh*, it has been largely given in all forms of *intestinal inflammation* and in *typhoid fever*. It has also been used externally as an antiseptic dressing, and as a local application in various skin diseases. It has certainly proved effective in many cases, but has been supplanted by naphthol, which is similar to it in action and probably more effective. The ordinary dose is from two to eight grains (0.12–0.5 Gm.), but as much as eighty grains (5.5 Gm.) per day are said to have been given with good results. It is best administered as a powder in capsules.

### BETANAPHTHOL.

Naphhtol is a phenol which is present in small quantities in coal-tar, but is usually prepared artificially by heating naphthalene with sulphuric acid and fusing the resulting naphthalin-sulphonic acids with alkaline hydrates. There are two naphthols, alpha and beta, of which betanaphthol is official. It occurs as colorless or pale buff crystalline laminæ, or as a white or yellowish-white crystalline powder, of a pungent but not persistent taste, and a faint odor suggesting phenol. It is permanent in the air, very slightly soluble in water, very freely soluble in alcohol.

**Therapeutics.**—Betanaphthol was introduced by Bouchard and Maximovitch into practical medicine as a germicide which might be used on or within the human body for the purpose of inhibiting the growth of disease-germs. It appears to be of only second rank as a germicide, but to have value on account of being nearly free from toxic powers in relation to the higher animals.

Experimenters are somewhat at variance in regard to the exact germicidal power of betanaphthol. According to Bouchard and Maximovitch, in the laboratory 1 to 3000 will kill some pathogenetic germs and greatly retard the growth of the bacilli of typhoid fever and of tuberculosis, while about three grains per quart will arrest putrefaction. The experiments of Surveyor and Harley, however, indicate that naphthol is less active as a germicide than is bismuth subnitrate. Bouchard and Maximovitch, in contrasting experiments, found that mercuric iodide is six times more antiseptic than betanaphthol, but that phenol is five times less antiseptic, and creosote four times less antiseptic. Weeks found that 1:10 solution of betanaphthol in either destroyed the *staphylococcus pyogenes* in thirty seconds. The toxic dose of betanaphthol was found to be 3.8 grains per kilo of the animal, making it two hundred and fifty-three times less poisonous than mercuric iodide. At this rate the poisonous dose for an ordinary man would be between three and four thousand grains. In the animals killed by it, death took place through an arrest of respiration, the heart retaining its activity.

In experiments made to determine whether digestion would be seriously interfered with by betanaphthol, Clarke found that it has

a very distinct retarding influence on the artificial digestion of egg albumin by peptic fluids, a very slight effect on the artificial digestion of milk by the same, and no effect at all on pancreatic digestion of milk or albumin, nor on the conversion of starch into sugar.

Externally, betanaphthol was first used in 1881 by Kaposi, of Vienna, who found it to be, when in solution in oil or alcohol, markedly irritating to the skin, 1 part to 100 distinctly affecting *eczematous eruptions*, and 1 to  $1\frac{1}{2}$  parts per 100 being sufficient to provoke urticaria on a healthy skin. In the form of soap, containing 2 parts per 100, Kaposi found it useful in *prurigo*, *ichthyosis*, *herpes*, and *favus*, obtaining in many cases the best results by alternating this soap with a sulphur soap, and avoiding in this way a cumulation in the system which he believed was possible by the absorption of the drug. The practice of Kaposi was followed by numerous dermatologists with success, and led to the use of the remedy locally in inflammation of the mucous membranes, such as *conjunctivitis*, *chronic laryngitis*, *otitis*, etc.

Bouchard introduced the internal use of the drug for the purposes of disinfecting pathological cavities, and for intestinal antiseptis, especially in typhoid fever. Following Bouchard, a large number of clinicians have reported excellent results from the administration of the drug in *typhoid fever*; it is affirmed that it lessens the diarrhœa and other local abdominal symptoms both in adults and children. The remedy has also come into use in cases of *dilatation of the stomach*, *intestinal dyspepsia*, *diarrhœa*, or *dysentery*, when it is desired to check fermentative changes in the alimentary canal without producing the astringent or sedative effects of bismuth salts. The slow injection into the trachea, drop by drop, during a half-hour, of two hundred to three hundred cubic centimetres of its solution (1 to 1000) is affirmed by Pignol to be a useful procedure in *pneumonia*. Teissier has given it intravenously; others have exhibited it by the mouth in epidemic *influenza* and low fevers for the relief of albuminuria; but these uses of it are of doubtful value. Larger doses than from three to four grains (0.20–0.25 Gm.), given in capsules every two hours, are likely to disturb the stomach.

BETOL of Sahli, or *Naphthalol* of Kobert, is  $\beta$ -naphthol ether salicylate, and occurs in small, white, resplendent, almost tasteless crystals, insoluble in water. It is a compound analogous to salol, but having the base of naphthol instead of phenol and yielding, in the intestinal juices, salicylic acid and naphthol. It contains ten per cent. less salicylic acid than does salol, and is of no value in rheumatism, but has been much used as an intestinal antiseptic, and has been highly recommended by Kobert in *gonorrhœa* and other forms of *cystitis*. Dose, five to fifteen grains (0.3–1.0 Gm.).

MENTHOL, or *Oil of Peppermint Camphor*, has obtained great notoriety as a local anesthetic, and, if freely rubbed upon a part, it undoubtedly will often relieve neuralgic pains when they are superficial and peripheral in their origin: its solution (2 to 10 grs.—f $\frac{3}{4}$ i water) is said also to be very effective in *pruritus ani*, *chronic painful*

*eczemas, urticaria, etc.* Its physiological action has been studied by Paolo Pellacani. In the frog it causes paralysis, first of the spinal centres and finally of the nerve-trunks. In the mammal both mobility and sensibility are depressed, the animal grows cold, and the respiration becomes slow and shallow. Small doses excite, larger paralyze the frog's heart. In the poisoned mammal there were very curious, unexplained rhythms of rise and fall of the blood-pressure.

Goldscheider has been led to the conclusion that the sensation of cold produced by the local application of menthol is due to a special influence exerted upon the special nerves of temperature by finding,—first, that after the application of a solution of menthol in lanolin the local temperature is increased 2° C., although a marked sensation of cold has been produced; and, secondly, that the cold is not due to evaporation, because covering the part to which the menthol is applied with a watch-glass does not affect the sensation. He also found that if the menthol ointment were applied to one side of the forehead, bodies which previously had caused the sensation of cold no longer did so, and that application of menthol produced a sensation of warmth upon the elbow and the volar side of the wrist, positions at which, according to Herzen, similar warm sensations are caused by pressure upon the nerve-trunks. I. Ioteyko found that the sensation of cold is preceded by loss of general sensibility, and that the maximum of cold and anesthesia correspond.

S. A. Russell affirms that menthol has a remarkable power of controlling superficial inflammations. He asserts that an ethereal solution, of the strength of from ten to fifty per cent., two or three times a day by means of a camel's-hair pencil, will control *boils, carbuncles, superficial abscesses, etc.* It is very largely employed, in conjunction with camphor, as a local application in *rhinitis* and *laryngitis*. Bishop recommends a solution containing ten per cent. of each drug; more commonly a one- to two-per-cent. solution in liquid petrolatum is used by atomization.

### THYMOL.

*Thymol* is a phenol found in the oil of thyme \* (*Thymus vulgaris*) and of some other plants. It occurs either as an uncrystallizable liquid or in white rhombic or acicular crystals.

#### Official Preparations:

Thymol.....	5 to 15 grains (0.3–1 Gm.).
Thymolis Iodidum.....	External use.
Liquor Antisepticus †.....	External use.

Thymol has been urged as a substitute for carbolic acid by Volkmann and Ranke, of Halle, but, although a powerful antiseptic, has not come largely into vogue. Its fragrant odor has proved a decided disadvantage, in summer at least, by attracting swarms of flies. It is not free from poisonous properties.

\* According to Cardeac and Meunier (*Journ. Med. Vet. Zootech.*, 1890), the physiological actions of the oils of *Thymus serpyllum* and *Thymus vulgaris* are the same; they produce in animals dilated pupils, staggering gait, hallucinations, loss of sensibility, muscular relaxation, insomnia, trembling, contractures, exceedingly rapid respiration, and death, preceded by complete muscular relaxation and anesthesia.

† A word concerning those two greatly overestimated preparations Liquor Antisepticus U.S.P. and Liquor Antisepticus alkalinus N.F. and their proprietary kin Listerine and Glycothy-



According to Sternberg a one-fourth-per-cent. solution of thymol in alcohol is equivalent in germicidal properties to one- and one-fourth-per-cent. solution of carbolic acid against the coccus of mouth septicæmia. Bucholz ranks thymol as about the same strength as salicylic acid.

It has been used internally by Bälz in doses of thirty grains a day, or less. In a few instances nausea and vomiting were caused. There were abundant sweating, singing in the ears, deafness, constriction in the forehead, reduction of temperature, and frequently diarrhœa. The urine was dark greenish, yellowish-brown by transmitted light, free from albumin, becoming cloudy and grayish-white on the addition of the tincture of the chloride of iron. Violent delirium occurred several times, also marked collapse, and, in one case of typhoid fever, unconsciousness, with most alarming collapse. Bälz concludes that the remedy is much less certain and more dangerous as an antipyretic than is salicylic acid.

The possession of poisonous properties by thymol has been confirmed by the experiments of B. Küssner. This observer found that when given to dogs and rabbits by the stomach the poison acts very slowly and feebly, on account of its slow absorption, but when injected into the circulation it produces death by failure of respiration. Post-mortem examination failed to detect fatty degeneration or other lesion in either the solid tissues or the blood. The continuous repeated exhibition of small doses of thymol had no perceptible effect, except to interfere in some way with nutrition, so that the animals lost flesh. Küssner has found that thymol has the power of dissolving the red blood-corpuscles.

Thymol is eliminated through the kidneys partly as thymol itself, partly as thymo-hydrochinone united with sulphuric acid, partly as a chromogen, which is probably an oxidation product of thymol, and partly as some acid of unknown constitution (F. Blum).

Thymol on account of its agreeable taste is largely employed as an antiseptic in diseased conditions of the mouth and throat. It is no longer used in *diabetes* as suggested by Küssner; \* nor as an intestinal antiseptic in *typhoid fever* as recommended by Martime and by F. P. Henry. It has been recommended by Fischer and others in *pertussis*. Thymol is also employed as an anthelmintic (see p. 646). Dose, fifteen to twenty grains (1-1.3 Gm.) in the twenty-four hours.

### RESORCINOL.

Resorcinol (*resorcin*), *pyrocatechin* and *hydroquinone*, are three dioxybenzols, resembling each other very closely in physiological effects, but of which only resorcinol is used in medicine. This occurs in colorless, short, aromatic prisms or plates of an unpleasantly sweet, somewhat acrid taste, which on exposure to the air becomes reddish. It is soluble in half of its weight of water, also in alcohol, or ether, and in about twenty parts of fixed oil.

**Physiological Action.**—*Local Action.*—*Elimination.*—Resorcinol is an active irritant, but is scarcely able to act as an escharotic. According to Joseph Schomacker, it is eliminated with the urine as a sulpho-acid, which on boiling with HCl is decomposed, resorcinol being set free; after very large doses, free resorcinol may be found in the urine. The excretion is said to be completed in about seven

moline may be in place here. The antiseptic power of any of these preparations is so extremely slight that they are practically worthless, except as more or less pleasant vehicles for mouth washes and gargles.

\* See Fürbringer (*Deutsches Archiv f. Klin. Med.*, xxi.).

hours. It is actively poisonous to the lower organisms, and, according to Martin Cohn and Andeer, a one-per-cent. solution of it is sufficient to arrest, for a long time, putrefactive changes in the urine, organic infusions, and even animal tissues. Platt states, however, that it is distinctly inferior to phenol as an antiseptic.

*General Effects.*—In doses of twenty to forty grains resorcinol causes flushing of the face, with giddiness, buzzing in the ears, and some quickening of the breathing and pulse, followed, after a time, by violent perspiration and sometimes depression of temperature.

Andeer took about one hundred and fifty grains of resorcinol, dissolved in a pint of water, during fifteen minutes. After disturbance of the cerebration and of the special senses, he fell into a condition of collapse, with cold extremities, epileptiform convulsions with loss of consciousness, opisthotonos, and marked disturbance of the respiration. Consciousness did not return for five hours. Murrell records a case in which a woman took one hundred and twenty grains of resorcinol, and immediately felt giddy, had sensation of pins and needles all over her, and a few minutes later was insensible, with closed eyes, clenched hands, pallid, blanched lips, dry tongue, normal pupils, and insensible conjunctiva; the temperature was 94° F.; the reflexes were entirely gone; the pulse was weak and thready. Jos. Loeffler reports the case of a woman, thirty-one years old, who, immediately after the injection into the stomach of two litres of a three-per-cent. solution of resorcinol, was seized with violent gastric pain, followed at once by unconsciousness, cyanotic face, and clonic contractions. In spite of the immediate removal, as far as possible, of the solution, the cyanosis became more intense, the unconsciousness and muscular relaxation complete, with, from time to time, active tremors; the pulse very small and frequent; the respiration completely arrested, with respiratory muscles in such a condition of tetanus as greatly to embarrass artificial respiration. Under the continued use of artificial respiration, however, recovery was finally secured. In several cases of children the washing out of the stomach with a three-per-cent. solution has been followed by collapse and death, and in one case hemoglobin was found in the urine.

In the lower animals (Dujardin-Beaumetz) resorcinol causes tremors, loss of consciousness, and epileptiform convulsions, which, when the dose has been sufficiently large, become more and more violent, until the increasing disturbance of breathing ends in respiratory arrest. During the spasms the temperature of the animal is distinctly elevated, but when there is quiet narcosis it may fall below normal. The urine becomes olive-green, deepening into blackish.

Resorcinol resembles phenol in being a universal poison, but is less active. It probably affects the nerve-centres as does phenol, and has been shown by Beyer to be a direct cardiac paralyzant.

*Therapeutics.*—Resorcinol is used almost solely as a topical remedy in diseases of the skin and mucous membranes. It has been highly recommended by Hoefel, Lichtheim, Janicke, Fliesburg, Baginsky,\* and others in various acute and subacute gastric or intestinal inflammations, such as *enteritis*, *gastric ulcer*, and *cholera infantum*, but in our experience has not given satisfaction. In *hay fever*, *chronic otitis*, *gonorrhœa*, *leucorrhœa*, and other mucous catarrhs, it may be applied locally in the solution of from one to fifteen-per-cent. The three- to five-per-cent solution has been largely used in

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\* See *Therap. Gaz.*, ii. and iii., and *Berliner Klinische Wochen.*, 1889, xxvi.

Germany in washing out diseased stomachs, but care is necessary to avoid poisoning. In chronic *cystitis* irrigation of the bladder with a three-per-cent. solution has been found effective.

It is said to be valuable in the treatment of the various parasitic skin diseases such as *tinea* and *scabies*. Too irritating for acute inflammations of the skin, it certainly exerts a powerful effect on recent cell infiltrations, and is extraordinarily successful in chronic and subacute *eczema*, where there is much thickening from exudation, in *seborrhæa*, and even in *psoriasis* and *pityriasis*. It is preferably used in solution; from ten to thirty grains in one drachm of alcohol, one drachm of glycerin, and eight drachms of water, well sopped on the part and allowed to dry. According to Andeer, resorcinol, in powder or in saturated ethereal solution, is a feeble caustic, useful in the treatment of *chancres*, of *papilloma*, and even of *epithelioma* and *diphtheria*. Dose, two to five grains (0.13–0.3 Gm.).

**OXALIC ACID.**—The chief interest of this substance to the medical profession is as a poison. Oxalic acid is a paralyzant to the respiratory, vaso-motor and spinal motor centres (Rabuteau and Kobert and Küssner). It is also a cardiac poison, arresting the heart in systole. The acid is eliminated by the kidneys. As a poison, oxalic acid figures in two forms: that of simple oxalic acid, and that of the *acid potassium oxalate*, or *salt of sorrel*, or *essential salt of lemons*, as it is variously termed in common parlance. The symptoms produced are a hot acrid taste experienced during the swallowing, a burning in the gullet, soon extending to the stomach, intense abdominal pain, vomiting of highly acid, greenish, blackish-brown or bloody mucus (rarely of arterial blood), collapse, livid surface, cold skin, entire prostration of strength, small, irregular pulse, stupor, unconsciousness, sometimes convulsions, and finally death. In some cases the gastric symptoms are very prominent; in others they are nearly wanting, and the chief manifestations are collapse and such nervous symptoms as almost complete general paralysis, numbness, and finally stupor; indeed, the patient may suddenly fall unconscious immediately after the ingestion of the poison. Nephritis and oxaluria are probably constant symptoms and glycosuria has been noted by Kobert and Küssner and by Sarganeck.\* In pregnant women abortion or at least death of the fœtus usually occurs.

Taylor states that the smallest quantity which is known to have caused death is one drachm. An ounce usually proves fatal, but has been recovered from. After death the coats of the stomach are found softened and swollen, and sometimes perforated. Rabuteau affirms that the blood is everywhere scarlet; but this is certainly not always the case (Taylor). According to Kobert and Küssner, a pathognomonic post-mortem lesion is the incrustation of the urinary tubules

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\* Kobert has made the very important observation, that the extract of *Syzygium jambolanum* will control the glycosuria produced by oxalic acid.



with crystals of oxalates. In poisoning by oxalic acid, the immediate administration of an antidote is of the utmost importance.

As the potassium and sodium oxalates are poisonous, neither potash nor soda is available; but, fortunately, lime or chalk is a perfect antidote to oxalic acid, forming the excessively insoluble calcium oxalate. As time is a matter of so much importance, tooth-powder, chalk, "whitewash" off a wall, or a fence, or whatever form of lime be at hand should be rubbed up with water and administered freely. The after-treatment is that of toxic gastro-enteritis.

As an emmenagogue, oxalic acid has been used in all forms of *amenorrhæa* with asserted great success. It is said also to be an active abortifacient, but as such is certainly extremely dangerous. The dose usually given is half a grain three or four times a day, but F. W. Talley has reported serious poisoning as produced by this amount.

Oxalic acid is a powerful germicide. According to O. Loew, the one-per-cent. solution of the neutral potassium oxalate is very active in the destruction of infusoria, while Howard A. Kelly asserts that potassium permanganate and oxalic acid afford the only known practical means of disinfecting the surgeon's hands.\*

### FORMALDEHYDE.

*Formaldehyde*, *formyl* or *formol*, is a gaseous body which is obtained by the oxidation of methylic alcohol at moderately high temperature, as by passing the vapors over red-hot metal or carbon. It readily dissolves in water and alcohol, forming a colorless fluid, having a peculiar, pungent odor and an unpleasant taste.

**SOLUTION OF FORMALDEHYDE** (*Liquor Formaldehydi*) contains not less than thirty-seven per cent., by weight, of absolute formaldehyde, which is the strongest permanent aqueous solution that can be made.

**Physiological Action.**—*Local Action.*—*Absorption and Elimination.*—Formaldehyde is an intensely active local irritant, producing even when in very minute amount in the air violent irritation of the respiratory mucous membrane, or, it may be, fatal pulmonary inflammation. It is also a very active coagulant of albumin and gelatin when in at all concentrated form; and when added to blood it causes an immediate coagulation, with a serum so strongly colored red as to suggest destruction of the red blood-corpuscles, though it may be that the color is due simply to the squeezing out of the corpuscles from the clot. According to Mosso and Paoletti, however, when added in a very dilute form to an albuminous solution, formaldehyde not only does not coagulate the albumin, but so acts as to prevent the coagulation of albumin by heat. It is therefore capable of absorption, and the statements made that the urine passed by animals to

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\* The method practised by Kelly is as follows: 1. Scrub the hands for ten minutes in hot water frequently changed. Immerse in a saturated solution of potassium permanganate, until every part of the hands and lower forearms is stained a deep mahogany red or almost black color, transfer to a saturated solution of oxalic acid until completely decolorized and of a healthy pink color. Wash off the oxalic acid in warm sterilized water.

which it is given even in moderate quantities is incapable of putrefaction indicate that it is not only absorbed, but also eliminated unchanged from the kidneys.

The discovery by Trillat, in 1888, that formaldehyde is a powerful germicide, has been abundantly confirmed, but its activity has been greatly overestimated. The more recent investigations indicate that it is not much stronger than is phenol.

According to Burgess, a two-per-cent. solution of formaldehyde kills the bacillus coli communis in five minutes. In the experiments of Slater and Rideal it required fifty minutes for a one-per-cent. solution to kill the staphylococcus pyogenes aureus or bacillus typhosus, and thirty minutes to destroy the bacillus coli communis. Clothing soaked twenty-four hours in a 1:1000 solution was not always sterile, but after being exposed to a one-per-cent. solution was always sterilized.

As regards the effect of the formaldehyde vapor in disinfecting a room, Slater and Rideal found that after the evaporation of one and one-half ounces of a forty-per-cent. formaldehyde solution in a room of fifteen hundred cubic feet there was a marked diminution of the number of organisms found in the dust, although they were not all destroyed. According to Trillat, one pound of a forty-per-cent. formaldehyde solution is sufficient to disinfect an ordinary-sized room. Kenwood has determined that when formaldehyde vapor is present in the air in the proportion of one and one-half to two per cent. there is complete and rapid disinfection of all the surfaces. Woodhead found that the vaporization of one pound of forty-per-cent. formaldehyde solution, by means of a special form of apparatus, destroyed all exposed cultures, including the spores of the anthrax bacillus, but that pieces of folded linen were not always completely sterile. In a lamp generating formaldehyde directly from methyl alcohol, according to Kenwood, it requires one and one-half litres of alcohol to disinfect a room of two thousand cubic feet. A popular and convenient form of formaldehyde generation is through the heating of tablets of *paraformaldehyde*. According to Rideal, one gramme per thousand cubic feet of paraform did not kill the bacillus coli communis in four hours. Four grammes per thousand cubic feet of air space killed the test-germs which were exposed on silk threads, but not cultures soaked into paper slips. Ten grammes of paraform per one thousand cubic feet killed various non-sporing micro-organisms, both exposed and when wrapped inside of rolls of linen. The spores of the anthrax bacillus and bacillus subtilis were usually but not invariably destroyed by twenty grammes per thousand cubic feet.

In an elaborate investigation made in 1903 by Ravenel and Gilliland the value of formaldehyde as a germicide was abundantly reaffirmed, and the importance of the abundance of moisture in the air with the formaldehyde vapor, and the value of high temperature when it can be obtained as assisting in the action of formaldehyde, were made very apparent. The theory of Van't Hoff, that formaldehyde acts as a bactericide by the formation of an active oxygen, has been disproven by Waldemar Koch, and it would appear that it acts directly.

According to the experiments of Aronson and of Burkhard formaldehyde not only is a germicide, but also has the power of destroying the toxins of diphtheria, of tetanus, and probably of other diseases.

*General Effects.*—The violent irritation produced by formaldehyde is so immediate that accidental or purposive poisoning by it is very rare. The general action of the drug is evidently feeble, as it produces more serious symptoms when given by the mouth than when injected hypodermically (Mosso and Paoletti).

Trillat states that sixty-six centigrammes of formalin per kilogramme given to the guinea-pig are not mortal, although the urine passed by the animal is incapable

of putrefaction; while the intravenous injection of thirty-eight centigrammes per kilogramme causes in the rabbit no pronounced symptoms. According to Mosso and Paoletti, fifty cubic centimetres per kilogramme injected hypodermically produce in the dog severe poisoning, with fall of temperature, ending after many days in death; the same amount given by the stomach causes in the dog violent convulsions, general rigidity, salivation, and in a short time death, preceded by stupor and unconsciousness.

In J. Klüber's case of poisoning the patient, a man, was found unconscious and supposed to be suffering from apoplexy. The coma lasted for many hours, going off gradually in a stupor. The urine was suppressed for nineteen hours, and formic acid, but neither sugar nor albumin, was found in it. L. Zorn reports a case with burning in the mouth and stomach, nausea, mild cyanosis, albuminuria, and difficulty of breathing.

According to Mosso and Paoletti, small doses cause rise in the blood-pressure, probably as the result of peripheral contractions of the arteries; while toxic doses depress the circulation and so act upon the blood that on exposure it coagulates instantly, with the separation of a dark red serum.

**Therapeutics.**—On account of the safety connected with its use, its activity, its permanence of constitution, and its lack of destructive action on vegetable and animal substances, formaldehyde is probably the most reliable and the most generally useful of all the germicides when it is not necessary to bring the agent in contact with the human body. It does not affect either the color or structure of clothing or other materials in common use. Its vapor, being of low specific gravity, mixes readily with the air, and penetrates loose fabrics much more deeply than does any other known germicide.

Using an apparatus invented by himself for the production of formaldehyde directly from methyl alcohol, Trillat found that it was possible completely to disinfect rooms and the furniture contained therein in six hours, by the consumption of from four to six litres of the alcohol for each three hundred cubic metres of the room. In 1895 Van Ermengen and E. Sugg sterilized in a room books and other small objects containing the germs of diphtheria, tuberculosis, scarlet fever, small-pox, etc., by means of formaldehyde evaporated from its aqueous solution in such quantity that there was about the value of five cubic centimetres of formaldehyde in one litre of air, and in 1896 it was demonstrated by E. G. Horton that infected books shut up in a closed space could be disinfected in fifteen minutes by the vapor of commercial formalin,—one cubic centimetre of the formalin to three hundred cubic centimetres or less of air,—and that the books were not in any way injured by the process. More recently there has been abundant confirmation as to the activity of formaldehyde, which, when properly used in a room with moistened air, fails only when the objects are so dense or in such mass that they cannot be penetrated.

It has been shown in an elaborate series of experiments by Herzog that the addition of formaldehyde vapor enormously increases the disinfective power of steam, but that this increase of power does not influence the disinfection of massive objects; the outer layers of the object apparently absorbing all the formaldehyde out of the vapor, so that inside of a bundle of blankets the effect would be simply that of pure moist heat. Vapor at 70° C., containing one per cent. of formaldehyde, was found to kill spores in four minutes which were able to resist the action of simple watery vapor at 98.5° C. for nine minutes without injury.



In disinfecting an apartment, windows, doors, chimneys, ventilators, and similar openings should be tightly closed, while the air should be made to contain at least one per cent. of formaldehyde gas, and at the end of twenty-four hours, when the apartment may be opened, should still be strongly impregnated. The gas may be obtained by the pulverization of formalin or other solution of formaldehyde, but not by the simple evaporation of the solution, since the formaldehyde, upon the application of heat, becomes largely polymerized into a solid, *paraform*,\* which gives off formaldehyde slowly and in small quantities. It is stated that the addition of glycerin to the solution of formaldehyde prevents the polymerization by heat of the formaldehyde, so that the so-called *glycoformalin* (formaldehyde thirty parts, water sixty parts, glycerin ten parts) is preferable to the aqueous solution, although its use has the distinct disadvantage of leaving many articles in the room sticky from a coating of glycerin.

The intense activity of formaldehyde as an irritant greatly interferes with its use upon the human body. The application to an ulcerated surface of even its one-per-cent. solution causes intense pain lasting for a considerable length of time. Nevertheless, formaldehyde is employed to a considerable extent by practical surgeons in cases of *tubercular abscesses*, *infected wounds*, and *infectious inflammations of the mucous membranes*. In many instances it is better to apply a strong solution once or twice than to use a weaker solution more frequently, although a one- to five-per-cent. solution is spoken of by various surgeons as singularly effective. By the previous application of cocaine the pain normally produced by the formaldehyde may be prevented, and there is no danger of systemic-poisoning by even the strongest solution. The two-per-cent. solution of formaldehyde is very effective for the disinfecting of the hands of the surgeon, but has been found too irritating to be practical. A one- to two-per-cent. solution is sometimes employed for the rendering of instruments aseptic, but its use is usually less convenient than that of a simple chamber in which by means of heated paraform the instruments may be disinfected. It is stated that by the employment of this apparatus instruments contained in a chamber one cubic foot may be absolutely disinfected in fifteen minutes by the evaporation of five grains of paraform at a cost of one cent.

The use of formaldehyde for the preservation of milk and other articles of food does not seem to us justifiable; although when employed in the proportion of 1:5000 to 1:10,000 it does not affect the taste. It has been shown by A. G. R. Foulerton † to make milk less digestible, and also by F. W. Tunnicliffe and O. Rosenheim to distinctly affect assimilation in weak children, and probably to increase the destruction of nitrogen. In all cases observed by these investigators the amount of lecithin in the feces was diminished by the formaldehyde.

Formaldehyde has been used to some extent in human medicine as a local germicide in various infective diseases, and as a caustic in inoperable *cancer*, also by inhalation in *pulmonary tuberculosis* and *chronic bronchitis*, but its value is questionable.

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\* Paraform, or polymerized formaldehyde, is a colorless, crystalline powder insoluble in water, of very stable constitution, which when heated slowly gives off formaldehyde gas.

† See also Bliss and Novy, *J. Ex. M.*, iv.

Formalin has been used as an intravascular germicide, but its value has not yet been determined. It does not seem probable, *a priori*, that the treatment should be beneficial because a quantity sufficient to exercise any distinct antiseptic action cannot be injected without jeopardizing life. In the investigations of Fortescue-Brickdale, intravascular injections of formaldehyde were of no service in rabbits infected with pneumococcus or with the anthrax germ; and similar results were reached by W. H. Park with rabbits infected with pneumococci and streptococci. C. C. Barrows, however, in one case of violent human *septicemia*, believed that life was saved by the intravenous injection of formaldehyde; and a similar case is reported by W. F. Honan. In these cases 500–700 C.c. of a solution of formalin (1:5000 sterile physiological salt solution) were thrown slowly into the veins.

**VOLATILE OILS.**—The general properties of volatile oils have been already mentioned in the section on Aromatics (see page 478). Cadeac and Meunier\* give the following table as representing the time which it requires the pure volatile oils to destroy the typhoid bacillus:

	At the End of		At the End of
Cinnamon of Ceylon .....	12 minutes	Geranium of France.....	50 minutes
Cloves.....	25 minutes	Zedoary.....	2 hours
Eugenol.....	30 minutes	Absinthe.....	4 hours
Thyme.....	35 minutes	Sandalwood.....	12 hours

### BENZOIN.

The concrete juice of *Styrax Benzoin*, a large tree, native of Siam. The drug is said to be obtained by incising the tree and allowing the juice to harden as it exudes. The finest specimens of benzoin consist of tears agglutinated together; the poorest, of brown or blackish masses without tears. The fracture is resinous, the surface of the tears smooth and whitish, the odor fragrant, the taste at first very slight, afterwards somewhat acid. The chief constituents of benzoin are resin and benzoic acid; cinnamic acid is also frequently present.

*Benzoic Acid* is obtained by sublimation of gum benzoin. As thus prepared, it is in white feathery crystals, of a silky lustre, a warm, peculiar taste, and a fragrant vanilla-like odor, due to the presence of a volatile oil, the pure acid being inodorous. It is almost insoluble in water but its ammonium and sodium salts are freely soluble.

Benzoic acid is widely distributed through the vegetable kingdom, constituting the peculiar principle of all true balsams, and is occasionally present in the urine of grass-eating animals. It is a normal constituent of castor, and has been detected by Seligsohn in the suprarenal capsules of an ox. It is used considerably in the arts, and for this purpose is prepared from the allied hippuric acid of horse urine, and also, it is said, from naphthalin: these forms of the acid should never be used medicinally.

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\* Quoted by Sternberg (Text Book of Bacteriology, N. Y., 1896, p. 199).

**Official Preparations:**

Tinctura Benzoini (20 per cent.)	1 to 1 fluidrachm (2-4 C.c.).
Tinctura Benzoini Composita (10 per cent.)	1 to 2 fluidrachms (4-8 C.c.).
Acidum Benzoicum	10 to 30 grains (0.6-2 Gm.).
Ammonii Benzoas	10 to 30 grains (0.6-2 Gm.).
Sodii Benzoas	10 to 30 grains (0.6-2 Gm.).

**Physiological Action.**—*Local Action.*—Benzoic acid, unless in large quantities and pure, is scarcely irritant to mucous membranes, on which, however, it exerts a distinctly alterative influence. As a germicide it is quite active, but less powerful than salicylic acid.

*Absorption and Elimination.*—Benzoic acid is absorbed rapidly, and, as was first discovered in dogs by Wöhler, and afterwards in man by Ure, it is eliminated chiefly from the kidneys, united with nitrogenous atoms, as *hippuric acid*.\*

It has not yet been determined where in the body the hippuric acid is formed, nor yet has the source of the nitrogen been made out. Lewandowsky in five experiments found that although an enormous amount of hippuric acid was excreted there was no lessening in the elimination of uric acid, and hence concludes that there is no relation between the formation of the two acids. It has been suggested by Kuhne and Hallwachs that the conversion occurs in the liver; but the researches of Meissner and Shepard appear to show that it really takes place in the kidneys.

The conversion does not happen in the intestines or in the blood, since after the exhibition of large doses of benzoic acid it alone can be detected in the blood; and after the administration to rabbits of large amounts of hippuric acid by the mouth, only traces of the latter, with large quantities of benzoic acid, can be found in the blood, although the hippuric acid appears in the urine;† further, moderate amounts of hippuric acid injected into the blood cause severe symptoms of poisoning, which is not true of benzoic acid. When benzoic acid is injected freely into the blood, a portion escapes through the kidneys unchanged.‡ G. Bunge and O. Schmiedeberg have also found that in the dogs with renal arteries tied no conversion of benzoic into hippuric acid occurs, but that tying of the ureters does not interfere with the change and have succeeded in converting benzoic into hippuric acid by passing blood containing benzoic acid, with or without glycocoll, slowly through the kidneys, removed from the body directly after death. From some of their experiments it would seem that the blood-corpuscles play an important rôle in the process, as when serum freed from blood-corpuscles was used, at most only a trace of hippuric acid was formed. According to Meissner and Shepard, sometimes the benzoic is converted into *succinic* instead of hippuric acid in man, and in chickens it is habitually changed into new products, one of which is nitrogenous.

**General Effects.**—The influence of benzoic acid upon the general system is very slight. The largest therapeutic doses never produce any symptoms, unless it be those of slight gastric irritation; a half-ounce of the acid taken by Schreiber in two days caused only an increased rapidity of the pulse-beat and moderate disturbance of digestion.

\* Gusseron found hippuric acid in the urine of a new-born child when benzoic acid had been given to the mother just before the birth (*Hoffmann und Schwalbe's Jahresb.*, 1879, 283). The experiments of Von Schrader and of Mosso (*Arch. Exper. Path. u. Pharm.*, 1889, xxvi.) seem to show that the whole of the ingested benzoic acid escapes with the urine.

† For a general summary, see paper by Van de Velde and Stokvis (*Arch. f. Exper. Path. u. Pharm.*, xvii, 189). V. Poulet (*Bull. Soc. de Méd. Prat.*, 1888) uses the *hippurate of lime and lithia*, affirming that they are much superior to the benzoates in *ammoniacal cystitis*.

‡ According to the experiments of Th. Weyl and B. von Anrep, if benzoic acid be given to man or animals in a febrile state a much larger proportion of it than usual is eliminated unchanged (*Hoffmann und Schwalbe's Jahresb.*, 1881, 447).



W. Grube states that in massive doses (1 to 5766 of the animal's weight) it produces intoxication, with disturbance of circulation and respiration, and paralysis of the hind feet, and that the antipyretic influence of benzoic acid is greater than that of salicylic acid.

*Nutrition.*—Some authorities have believed that benzoic acid distinctly affects nutrition, but the testimony as to the action of the acid upon the elimination of urea and uric acid is so contradictory as to indicate that it has no constant powerful influence upon protoplasmic activities or upon nitrogenous elimination.

Ure, Leroy d'Etoilles, and Debouy (quoted by Stillé) affirm that the uric acid is very much diminished or altogether absent, while Garrod and Keller assert that its quantity remains normal. Again, Garrod affirms that the urea is very much diminished in quantity, Keller and Meissner and Shepard declare that it is not affected, and in the elaborate experiments of Carl Virchow, sodium benzoate caused a decided increase of the nitrogenous elimination from the kidneys.

It is commonly asserted by clinicians that the acidity of the urine is increased by the administration of benzoic acid, and it is probable that the disappearance of uric acid crystals from the urine under the influence of the drug is due to the conversion of insoluble uric into soluble hippuric acid. W. W. Ashhurst asserts as the results of experiments made with sodium benzoate, that this salt does not increase the acidity of the urine, and that the mistake of clinicians has arisen from the fact that in cystitis the urine has its acidity increased by the drug because the ammoniacal fermentation is checked by the benzoic acid.

*Antiseptic Influence.*—In April, 1872, Dougall announced that benzoic acid is an active antiseptic. Since that time, numerous experiments have been made by E. Salkowski, Grube, Bucholz, and Fleck, with the unanimous result of ascribing to benzoic acid a first rank in destroying bacteria and preventing putrefaction. In most of these investigations benzoic acid was shown to be much more active than salicylic acid. Bucholz found that 0.02 per cent. of benzoic acid has a very perceptible effect upon the development of bacteria, and 0.1 per cent. inhibits their growth entirely; also that the sodium benzoate is no less powerful than the pure acid. Kumagawa determined that benzoic acid acts powerfully as an intestinal antiseptic, notably reducing both the indican in the urine and the number of the bacteria in the intestines.

*Therapeutics.*—Benzoic acid is a valuable remedy in subacute nasal and respiratory catarrhs, also in chronic bronchitis. As an antizymotic it is considerably used by the Germans in diphtheria, erysipelas, and allied diseases. Senator, of Berlin, alleges that in daily doses of about three drachms it is equal in acute rheumatism to salicylic acid. Ure first suggested the employment of benzoic acid in uric acid gravel and calculus, because, as he thought, it diminished the excretion of uric acid; and Golding Bird subsequently asserted that his clinical experience had shown the value of benzoic acid in uric

*acid diathesis*. It certainly is often effective in causing uric acid crystals to disappear from the urine. In the *phosphatic urine* of *vesical catarrh* benzoic acid often acts most happily: it checks fermentation in the urine, aids in the solution of the phosphates, and acts upon the mucous membrane of the bladder as an alterative antiseptic. In *ammoniacal cystitis* the drug is of great value. It is also said often to act very happily in acute *gonorrhœa*.

Benzoic acid has the property of preventing animal fats from becoming rancid, and is therefore much used as an addition to ointments. Moreover, it exerts a peculiar, often very beneficial, stimulant action upon the skin, and is very useful in such conditions as *chapped hands*, lips, or nipples, and even in *fissure* of the *anus*.

There would seem to be no doubt that benzoic acid may be substituted for phenol or salicylic acid in antiseptic surgery. Under the name of *balsamum traumaticum*, a preparation practically the same as the compound tincture of benzoin, was formerly much used as a vulnerary. The practice has gone out of vogue, but the discoveries concerning antiseptics show that it was well founded.

CINNAMIC ACID is present in Peru and Tolu Balsam, but for commercial purposes is prepared synthetically. It is insoluble in cold water, but freely soluble in boiling water and alcohol. It has been used in medicine solely in the treatment of *tuberculosis*, especially in the form of *sodium cinnamate* (*Hetol*).

As originally suggested by A. Landerer, the salt is to be given intravenously, and, according to Tobias, the same vein may be injected from fifty to sixty times in succession. Most extraordinary results have been claimed for the method, Landerer affirming that in the early stages of uncomplicated tuberculosis eighty-five per cent. of the cases can be cured. The heated controversy which Landerer's paper gave rise to has been well reviewed by W. J. Robinson. It does not appear probable that the Landerer treatment will accomplish what is claimed for it, and the conclusion of Robinson, that sodium cinnamate is not a direct curative agent in tuberculosis, and is of no more value, symptomatically, than is creosote, is probably correct. The sodium cinnamate may be given by the mouth in doses of from two to three grains. The initial dose of the intravenous treatment should not exceed one-fiftieth of a grain; the injection may be made every third day, and the amount increased until one-third of a grain has been reached. A ten-per-cent. solution in glycerin affords an excellent method of administration.

## VI.—SULPHUR AND BORON COMPOUNDS.

### SULPHUR.

Sulphur\* is a yellow amorphous solid insoluble in water, but soluble in alkaline solutions, alcohol, the fixed and volatile oils, chloroform, ether, etc.

#### Official Preparations:

Sulphur Sublimatum.....	} As an alternative, 10 to 20 grains (0.6-1.2 Gm.)
Sulphur Lotum.....	
Sulphur Præcipitatum.....	
Unguentum Sulphuris (15 per cent.).....	External use.
Sulphuris Iodidum.....	Not used internally.

\* For an account of the various allotropic forms of sulphur, and its chemical properties, the reader is referred to works on chemistry.

**Physiological Action.**—Sulphur, itself, is probably an inert substance. Such changes as occur after its introduction into the intestinal tract are probably due to the formation of hydrogen sulphide.

When in sufficient quantity, sulphur acts as a mild laxative, producing soft, semi-liquid, feculent stools, accompanied generally by much offensive flatus of sulphuretted hydrogen. It is affirmed that in some instances the latter gas has been so freely generated and absorbed as to cause systemic poisoning. Its continued use has perhaps some effect upon nutrition; the secretions generally are slightly increased, and some have affirmed that the temperature is somewhat elevated; but the truth of this is certainly very doubtful. The oxides it forms are, however, at least locally, active bodies.

**Therapeutics.**—As an habitual laxative, sulphur has been used with asserted advantage in cases of *hemorrhoids* and of chronic *rheumatism*. It has also been employed as an alterative in both *rheumatic* and *skin diseases*. It is affirmed by Doit that the natural sulphur-waters are of very great value in the treatment of chronic *syphilis*, as they undoubtedly are in chronic *gout* and *rheumatism*.

The known germicidal properties of the sulphur compounds indicate that it should have value as an intestinal germicide, and it has been found to be of very great service by the U. S. medical officers in the Philippines in the treatment of the chronic *amœboid dysentery* of that country. It has also been highly commended by Woroschilsky in *typhoid fever*. In either case from ten to fifteen grains may be given in capsules every three to four hours.

Sulphur is chiefly used as a parasiticide in cases of *itch* and other skin infections.

**SULPHURATED LIME.**—*Calx Sulphurata.*—*Commercial Calcium Sulphide.*—A mixture containing, according to the requirements of the U. S. Pharmacopœia, at least fifty-five per cent. of calcium sulphide together with unchanged calcium sulphate and carbon in varying proportions. It has been strongly recommended by Sydney Ringer, by Duhring and others, for the treatment of successive crops of *boils*, and in *scrofulous* and other unhealthy sores and glandular enlargements in children. Official dose, one grain (0.06 Gm.).

### SULPHUROUS ACID.

*Sulphurous Acid* of the U. S. Pharmacopœia is a six-per-cent. (by weight) solution of sulphur dioxide (sulphurous acid gas) in water. It is a colorless liquid, with an acrid sulphurous taste, and the characteristic odor of burning sulphur. A somewhat elaborate study of the action of the sulphites upon vertebrata has been made by Pfeiffer, who finds that they are poisonous when in very large doses, but that the rapidity with which they are oxidized into the sulphate frequently brings about sudden recovery in the deepest condition of poisoning. In sufficient amount they are said to paralyze the blood-vessels, the heart, and the respiratory apparatus.

#### Official Preparations:

Acidum Sulphurosum.....	Not used internally.
Sodii Sulphis.....	15 to 60 grains (1-4 Gm.).
Sodii Bisulphis.....	10 to 30 grains (0.6-2 Gm.).



Sulphurous acid and its salts are most efficient in destroying the low forms of life which are connected with putrefaction and fermentation, and for this reason are preservatives of organic matters; they are also among the oldest of disinfectants, having been used as long ago as 1771; but recent experimental evidence indicates that they have not the great superiority which has been attributed to them.

According to the experiments of Sternberg, 1 volume of sulphurous acid gas in 100 volumes of air is sufficient to disinfect dry vaccine matter. As these experiments are in accord with older observations, they may be considered as correct.

According to Wernitz, the action of pepsin, of ptyalin, of invertin, and of diastase is prevented by the presence of an aqueous solution of sulphur dioxide of 1:1317 to 1:8600 (by weight); while the action of myrosin and of emulsin is neutralized by 1:21,000. Wernitz further says that strips of woollen or cotton goods saturated with putrefactive matter are disinfected by exposure of from four to six hours to an atmosphere containing four per cent. of sulphur dioxide. The very elaborate experiments of Koch, of Wolffhügel, and of Sternberg have shown, however, that when the infectious material contains spores sulphur dioxide is of very little efficiency.

Sulphurous acid may be produced very cheaply upon a large scale by the burning of sulphur, and its vapor when thrown with steam into the hold of a vessel mixes with the water of the vessel and with the condensing steam, penetrating into all the cracks and places where the disease-germs may have found resting-place. It does not readily undergo decomposition; its ordinary salts are germicidal, and it is still relied upon for the disinfection of infected ships. On the other hand, in an ordinary room it does not find water in which to dissolve; it is liable seriously to impair clothing, bedclothing, and other organic material of value; and as formerly made, by burning in a simple iron pot, it was ineffective; so that the purification of apartments by burning sulphur in the house has been entirely displaced by the use of formaldehyde.

The *sulphites* and *bisulphites* have been largely employed to arrest or control fermentation, and are useful in saturated solution in various parasitic diseases of the skin.

### BORIC ACID.

Boric (or *Boracic*) acid crystallizes in white translucent scales, soluble in eighteen parts of cold water, much more soluble in boiling water, which on cooling precipitates all but about twenty-three grains to the fluidounce. Hot glycerin dissolves and holds upon cooling as much as three drachms to the fluidounce. Sodium Borate occurs in white, flattened, prismatic crystals, soluble in seventeen parts of cold water. A. Dujardin states that borax is incompatible with the alkaloids.

#### Official Preparations:

Acidum Boricum.....	10 to 20 grains (0.6-1.2 Gm.).
Glyceritum Boroglycerini (31 per cent.)....	External use.
Sodii Boras [Borax].....	15 to 30 grains (1-2 Gm.).

**Physiological Action.**—*Local Action.*—Locally, boric acid is, when in concentrated form, distinctly irritant; in dilute solution, stimulant and antiseptic, and having even a soothing influence upon mucous membranes. Its sodium salt even in concentrated form is scarcely irritant. The germicidal power of boric acid and its salts is too feeble to be relied upon in cases of serious infection.

In 1874 Dumas and Schnatzles announced that borax is poisonous to the lower forms of life. In Bucholz's experiments, 0.75 per cent. of boric acid was found sufficient to prevent the development of bacteria. In the experiments of Walb, a two-per-cent. solution of borax distinctly checked the putrefaction of solution of fibrin; a five-per-cent. solution kept the solution fresh for nineteen days. Fresh muscle-fibres from oxen were kept fresh many days by a one-per-cent. solution. Sternberg found that boric acid and sodium borate are inefficient as germ-destroyers, but have considerable antiseptic power. The experiments of Sternberg have received corroboration from E. Andrews.

*Absorption and Elimination.*—Boric acid and its soluble salts are freely absorbed and eliminated, escaping to some extent with the perspiration, saliva, and feces, but chiefly through the kidneys. In the elaborate experiments of Chittenden and Gies, twenty-four to thirty-six hours were found to be generally sufficient for the complete removal of the drug, which showed no tendency to accumulate in the body. W. Straub, on the other hand, affirms that twelve hours are required for the elimination of half, two to three days for the complete throwing off the whole of the single large dose.

*General Effects.*—The general physiological action of boric acid and its salts is very feeble; doses of one hundred and fifty grains of borax a day ordinarily producing no distinct symptoms.\* Poisoning has, however, resulted from the too free use of the drug; the symptoms have varied somewhat, but in most if not all the cases there have been great depression of spirits, fall of bodily temperature, a very feeble pulse,—rapid or slow,—and an erythematous or a papulo-vesicular eruption accompanied by much swelling of the parts, and especially affecting the lower extremities and followed by exfoliation; nausea, violent vomiting, and hiccough have been present in some cases; ecchymoses have been noted; the mind usually remains clear until late in the poisoning, but death has been preceded by coma, with disturbances of the respiration and involuntary discharges.†

Serious boric-acid poisoning is very rare, and we have no knowledge as to the amount required to cause death.‡ The cases whose report we have met with are: George T. Welch, two ounces of boric acid in the vagina,—recovery; Mododewkow, death from washing out internal cavities with five-per-cent. solution; Hogner, death from washing the stomach with two- and a half-per-cent. solution.

\* G. Lemoine reports (*Bull. Gén. Thérap.*, May, 1892) a bluish-gray line, like that of lead poisoning, as present upon the gums in cases of epilepsy in which borax had been given very freely and continuously.

† A very curious effect is said (Schiff, *Rev. Méd. de Suisse Rom.*, 1881, 244) to be produced by the local application of boric acid to nerves: the part affected is affirmed to lose its power of originating but not of transmitting impulses, so that if the galvanic current be applied to the part of the nerve which has been exposed to the drug no muscular contractions result, but if the poles be placed above this part the distal muscles respond at once.

‡ For mild cases see *T. G.*, Oct., 1901; also McWalter, *L. L.*, Aug., 10, 1907.

In the experiments made by H. C. Wood and E. T. Stewart, enormous doses of boric acid salts were found to cause in the frog paralysis of voluntary motion and reflex activity, due to the depression of motor spinal-centres, the nerves and muscles not being affected. The saturated solution of sodium quadriborate, brought into direct contact with the heart, was feebly depressant, and, injected in enormous amount into the jugular vein of the mammal, it lowered arterial pressure.

The use of boric acid as a *food preservative* is a subject of great importance, involving enormous commercial interests. In this connection, however, it cannot be treated in full detail, but we give the following outline of the present evidence:

Boric acid is undoubtedly in sufficient dose capable of killing the lower animals, such as fish and frogs, but Liebreich has found that acetic acid is at least twenty times as poisonous to fish; and Th. Maass, that common salt is twice as toxic to the frog. Given in sufficient amount to mammals it is apt to cause gastro-intestinal irritation, but E. de Cyon found that borax added to meat may be given to the dog up to one hundred and eighty grains a day without disturbance of the general nutrition. The question involved in the present discussion is, however, not so much the effect of the single large dose of boric acid as the influence of the continuous use of the drug by man in small quantity. In the experiments of Chittenden and Giess 1.3 per cent. of boric acid added to the food of dogs caused no albuminuria, no disturbance of the proteid metabolism, and only slight vomiting—the animals gaining weight rather than losing under continuance of the diet; one hundred and fifty grains of borax per day failed to produce in the dog abnormal urine. Moreover, Liebreich found that in rabbits killed by borax the kidney structure was intact. On the other hand, Jacob Plaut affirmed that boric acid will produce acute parenchymatous nephritis, and Ch. Féré has seen albuminuria, uremia, and death in cases of human epilepsy in which borax had been given continuously for a length of time. Harrington maintains that the failure to produce toxic effects with boron derivatives is due to too short periods of observation. He experimented on cats to which were administered, over a period of one hundred and thirty-three days, from 0.5–0.8 gramme of borax. At the end of this period every animal, except one which had received 0.54 gramme daily, showed pathological changes in the kidney. In the studies of Polli eight persons took for forty-five days thirty grains daily of boric acid, and then for twenty-three days sixty grains daily without any abnormal symptoms being produced. In the investigation made for the United States Department of Agriculture by H. W. Wiley twelve young men were placed under observation for repeated periods of thirty to seventy days. Each period was divided into three stages: the fore-period, in which the patient was kept on a selected diet in a condition of nitrogenous equilibrium, the borax-period in which the same diet was continued with the administration of definite quantities of borax or boric acid, and the after-period following the withdrawal of the preservatives. There was found a diminution in the quantity of nitrogen eliminated by the urine, which continued in the after-period, and a distinct augmentation in the amount of phosphoric acid in the urine, with loss of bodily weight brought about by borax. The total solids of the feces were increased and the total solids of the urine diminished during the borax periods, and this relation lasted also into the after-periods. Taken in conjunction with the loss of bodily weight, which was an almost constant symptom, these results show that the borax had the effect of lessening the assimilation of food, very probably through the disturbance of the digestive processes, since when more than four or five grammes (one drachm) of borax were taken daily there were distinct symptoms of gastric disturbance. Wiley concludes that while the normal man can receive quantities of boric acid or borax, amounting to one-half gramme daily, for a limited period of time without loss of health, the long continued use



of the salts of boric acid creates disturbances of the appetite and digestion. The results of Wiley, so far as nitrogen elimination is concerned, are in disagreement with those of Gruber, who found that after large doses (5-10 grammes daily) there is an increased elimination of nitrogen, phosphoric acid, and sulphuric acid. This has been confirmed by Chittenden and Gies. They state that if the doses of boric acid did not decidedly exceed fifty grains a day, no influence was exerted upon proteid metabolism or the general bodily nutrition, or the kidneys.

The above summary of the present knowledge shows that the evidence in regard to the propriety of using boric acid as a food preservative is, as in most questions involving enormous pecuniary interests, more or less contradictory, but apparently demonstrates that foods preserved by boric acid are much inferior to fresh foods. How far, if at all, they are inferior to foods preserved by sodium chloride, and especially by potassium nitrate, is uncertain. It seems to us doubtful whether boric acid is more deleterious than is saltpetre. The fact is that all salt foods are of difficult digestion, and that both boric acid and saltpetre are irritant to the kidneys.\*

**Therapeutics.**—As originally suggested by Rosenthal, boric acid has been found to be an efficient remedy in *cystitis* with ammoniacal urine, rendering the urine acid probably by checking the fermentation. In our own practice great relief has been obtained in the *cystitis of spinal diseases* by washing out the bladder with a few ounces of a saturated solution of boric acid after the use of the catheter. As a disinfectant and soothing wash its solution is much used in *conjunctivitis* and *rhinitis*—from five grains to the ounce up to saturation. Boric acid is also employed as an antiseptic dressing to fresh wounds, abscesses, old burns, etc. (See M. Greene.)

The saturated solution of boric acid has been especially recommended in phlegmonous *erysipelas*. Both boric acid and borax are of excellent service in *aphthous ulceration*, *diphtheria*, and other *inflammations of the mouth*, in which crystals of the salt may be allowed slowly to dissolve in the mouth. C. F. Folsom has strongly recommended borax in the dose of fifteen grains three times a day in *epilepsy*. We have tried the remedy carefully in a large number of cases, increasing the dose until pronounced gastro-intestinal irritation was caused, without affecting perceptibly the return or the severity of the paroxysms.

### PRACTICAL DISINFECTION.

It is not proposed to discuss here the many larger questions in regard to disinfection, such as the proper care of sewerage, which belongs to the province of the sanitary engineer rather than to the daily routine of the medical practitioner. It may be well, however, to point out that while foul water-closets in cities have long been the subject of much attention and discussion, in country districts privies

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\* The most important recent publications opposed to the use of boric acid are *Borsäure als Konservierungsmittel* (E. Rost, Berlin, 1903); Wiley, United States Department of Agriculture, Bureau of Chemistry, Bulletin No. 84. In favor of it: *Boron Food Preservatives*, Perkins, Bacon & Co., Fleet Street, London; *Borax and Boracic Acid* (Oscar Liebreich, Berlin, 1899); *Wirkung der Borsäure und des Borax* (Oscar Liebreich, Berlin, 1903).

are usually left to their own noisome devices; a condition of total depravity which can be readily prevented by simply standing in the outhouse a barrel containing one part of lime mixed with three or four parts of dry earth; a small shovelful to be thrown into the receptacle immediately after use; and by the periodical withdrawal of the comparatively inoffensive mass resulting.

The problems of the practical physician, so far as disinfection is concerned, are three in number, as follows:

First.—*The preparation of the room for the reception of the person suffering from contagious disease.* All closets should be emptied, all articles of ornament and unnecessary furniture should be removed, and such as is allowed to remain should be free from upholstery, and drawers or other receptacles be kept as empty as may be. Carpets should be reduced to a single small rug or removed altogether, the nurse finding protection for her feet in cold weather by heavily lined, soft, high slippers. The ceiling, walls, surbases, floor, and closets, should be thoroughly cleaned with abundant soap, washing-soda, and hot water, special care being taken with all crevices or joints.

Second.—*Disinfection during occupancy of the room by the patient.* It is now generally recognized that to attempt the destruction in the air of the widely spread germs, such, for example, as exist in a small-pox epidemic, is childish, but it is not so universally recognized that the effort to destroy organic germs in the air of the room during occupancy is equally futile. No person can live in an air which contains any known germicide in sufficient amount to kill disease germs; and the putting of saucers or other receptacles of chlorinated lime about a sick room is a medieval barbarity which should never be permitted, because it tends to the production of a false sense of security. The air of the sick-room must be kept pure by the checking of the discharge into it of the disease germs, but especially and chiefly by free ventilation, not from one room into another, but directly in some way into the open air, so that the disease germs may be widely distributed and the patient supplied with an abundance of proper breathing material. The source of the poisonous germs is the body of the patient, and it is a matter of the most vital importance to destroy these germs as largely as possible at the point of discharge. In many contagious diseases the pathogenetic organisms are thrown off in large quantities with the urinary and fecal discharges; often they escape through the skin and through the sputum or other infected discharges from the body. All such excretions should be poisoned as soon as they leave the body; the disinfectant should be placed in the receptacle *before*, not after, it is used. Moreover, the discharges should be allowed to stand mixed with the concentrated germicide until sufficient time has elapsed for it to kill the organisms. Chamber-pots and other receptacles should not be immediately emptied after use. To allow any excretion, sputum, or other infected discharge to exist for a moment undisturbed is most culpable neglect. *Spit-cups, urinals, etc., should have the disinfectant in them while waiting for use.*

As the skin is often the channel of elimination of the disease poison, frequent washing of the patient is essential, and care must be taken that the water which has been used should not be emptied before it has been disinfected.

Of all the germicides, by reason of its cheapness and efficiency, chlorinated lime is usually preferable for the disinfection of germs in discharges. Phenol or formaldehyde may be used. Corrosive sublimate, on account of the ease of its decomposition and of the danger of having its solution about the sick room, is scarcely applicable to the present purpose. As the cost of chlorinated lime is practically nothing it should be used very freely.

The clothing of the patient should be cotton, and with the sheets often changed. In the changing it suffices to place a clean sheet upon the floor and throw into it the discarded clothing and bedding, then tie the whole into a hard ball and drop it into boiling water without opening, and allow it to remain for over half an hour until all organisms have been destroyed. This method has, however, the objection of fixing permanently in the muslin all stains from blood, feces, and organic discharges. It is better, therefore, and in a hospital-ward it is essential, to throw the personal and bedclothing piece by piece when taken off directly into a covered vessel containing a disinfecting solution. According to the experiments of A. C. Abbott, corrosive sublimate is actively mordant, and should not be used. Chlorinated lime, 0.5-per-cent. solution, in cold water, is effective, does not fix stains, and though theoretically it should attack the structure of various fabrics, practically has no perceptible influence unless after repeated immersion. Probably the best disinfectant solution for this use consists of formaldehyde, three parts; common soft soap, three parts; cold water, one hundred parts. After two hours' soaking in such a mixture the clothing must be taken out and well washed in water at a temperature *not exceeding* 100° F. until all stains have been removed.

Absolute cleanliness in regard to the room itself must be strictly enforced during the whole period of sickness, and in many cases it is advisable to mop the floor, surbases, windows, etc., with water containing ten per cent. of formaldehyde.

Third.—*Disinfection of apartments that have been used.* The process of purifying an infected room naturally divides itself into two parts,—first, the killing of the germs; second, the cleaning of the room; and these two acts should always follow in the order here given so as to lessen as much as possible the danger to the operator and to the surrounding habitations which would be caused by the dispersion of the active germs. When the room has been thoroughly prepared and properly taken care of during its occupancy its purification is very simple. First, all clothing and bedding must be disinfected, and the most efficient and useful agent in so doing is heat. In cities, in quarantine stations, and other places where proper apparatus is forthcoming, all articles of the character spoken of should be exposed



to the prolonged effect of hot steam in closed chambers. When this is not possible, whatever can be boiled without injury should be boiled for at least forty minutes. Such articles as cannot be boiled may be immersed in a 1:1000 solution of corrosive sublimate over night, or preferably in a two-per-cent. formaldehyde solution, and then thoroughly washed. To those articles of clothing or bedding to which none of these processes are available without serious injury, fire should be applied if the infection has been at all severe. All articles of furniture should be washed with a solution of corrosive sublimate, 1:500, care being taken to see that the solution is well applied to cracks, joints, etc. Twenty-four hours later the furniture may be sponged off with an ordinary solution of soap and water.

In the further purification of the room, it must be remembered that it is not chiefly the air which is to be purified but the various solid surfaces and bodies on which germs have found lodgement. The best of the germicides for this purpose is undoubtedly formaldehyde. It is used in practice in various ways. It is demonstrated that the moist gas acts very much better than does the dry, and in our opinion the best method of applying formaldehyde is by means of a spray or atomizing apparatus, which should throw a finely broken spray all over the subbases, walls, floors, etc., so as to bring the formaldehyde in direct contact with the infected surfaces in excessive amount. The ordinary spray pump used by fruit-growers suffices for an impromptu disinfection, but is better replaced by a special atomizer when much work is to be done. The rule of the Philadelphia Health Bureau in regard to the strength and amount of the solution to be used seems to us correct. A solution of equal parts of water and of the official watery solution of formaldehyde is sprayed upon all the surfaces of the room in the proportion of three pints of the solution to one thousand cubic feet of air space in the room.

In lecture-rooms, with abundant benches, and in some other peculiar apartments, it is possible that this amount of solution would not suffice to cover all surfaces. Under these circumstances sufficient of the disinfecting fluid should be used to wet every surface in the room. We are informed by Dr. A. C. Abbott, chief of the Philadelphia Health Bureau, that they secure by means of the solution, sprayed in the manner above related, one hundred per cent. of disinfection, that is to say all test objects placed in a room have their germs destroyed by it. It is essential that the work be done quickly, and in very large rooms several operators should work at the same time; since the liberation and diffusion of the formaldehyde gas will very soon drive the operators from the chamber.

By means of the formaldehyde lamp, or various vaporizers, it is possible to disinfect the apartment without the direct use of atomization. If the atomizer be used, one part of a saturated solution of formaldehyde may be added to four parts of water, so as to make a twenty-per-cent. solution. After the treated room has been shut twenty-four hours it may be opened, freely ventilated, and *thoroughly* cleaned with abundant use of fresh water, soap, washing soda, scrubbing-brush, and physical exercise.

When it is necessary to disinfect a room which has not been properly prepared or taken care of during a past illness, the method of procedure is in general similar to that just described, but different in some minor details. All small articles which can be without injury purified by heat, either in the steam-chest or by boiling, should be so treated. All articles which cannot be so acted upon without injury should be, with the furniture, well washed with the corrosive sublimate solution; or if the character of the articles forbids this, may be disinfected with formaldehyde. For this purpose the articles must be taken out of the drawers and placed in position where they will be fully exposed in all their surfaces during the process. Books should be set upright on tables, and opened as widely and freely as possible, so the leaves hang loose and separate. Engravings and paintings may be freely exposed by the removal of the glass-covering or other method to the action of the formaldehyde, and should in the case of paintings be sponged carefully with lukewarm water immediately after being exposed to the fumes of the formaldehyde. Corrosive sublimate is not to be used on metallic articles, or of those of marble or other lime salt; these substances are not, however, affected by formaldehyde. The cleaning of the room after disinfection should be extremely thorough.

Prisons, hospital-wards, houses which have been inhabited by tuberculous patients, and other edifices, are liable to become so infected with organisms, especially with tubercular organisms, that the processes detailed are not sufficient. Frequently such buildings are more or less out of repair; when this is the case, all decomposed wood should be torn out and left out during the process of disinfection. (See below.) Moreover, not rarely in these buildings the most rigid disinfection will fail to destroy germs which work their way into absorbent walls or wood surfaces or deep crevices, so that scraping off of the plaster and tearing out of the rooms may be necessary for the purification of the apartment. If the germs are active, as are those of typhus fever, in order to protect the workmen, a superficial disinfection should precede these destructive acts. In many of these cases the first stage of disinfection should consist of a free application, by means of mops, of a four-per-cent. solution of sodium hydroxide to ceilings, walls, surbases, floors, sinks, drains. Such a hot alkaline solution acts very decidedly upon the germs themselves and rapidly destroys all kinds of filth, and thereby exposes the germs to the after-action of more generally recognized germicides. A day or two after the use of the soda the apartment should be thoroughly washed out with plain warm water. When there are wide cracks or crevices, corrosive sublimate solution,\* 1:200, should be freely used *before* the alkaline solution, which will decompose and render innocuous

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\* In this, as in many other cases, when there is danger of corrosive sublimate being decomposed by organic or alkaline substances, the solution is made more effective by the use of hydrochloric acid. Half an ounce of mercuric chloride, two ounces of strong hydrochloric acid, and three gallons of water, make a very effective solution, not so readily decomposed as the simple mercuric chloride.

any excess of the mercuric chloride. Whenever there is a metal surface, such as occurs in sinks, drains, pipes, etc., a five-per-cent. cresol solution is preferable to the corrosive sublimate; or a ten-per-cent. solution of formaldehyde may be used. After the processes spoken of have been carried out, the final disinfection may be made by mopping out with large quantities of the formaldehyde solution; or in some instances chlorinated or formaldehyde lime-wash, as detailed below, is preferable.

Formaldehyde vapor is often used, but is less effective than the application in mass of formaldehyde solution to the various surfaces.

*Infected stables* offer problems different from those of ordinary buildings; the tetanus germ exists in the soil, and when the infection of the stable is with this bacillus, the removal of the animals to another locality and the torch are almost the only resource. The products of animal and vegetable decomposition are so abundant about stables that corrosive sublimate is of very little use, except for washing off mangers and similar objects. Further, in the case of dairy stables, phenol, chlorine, and other disinfectants which have strong and persistent odors, cannot well be employed because they are liable to damage the milk for a long time after their use. The first step in the disinfection of a stable is the removal and destruction of all rubbish, loose boards, and decomposed wood. Then the absolute cleaning-up of the stable with a solution of sodium carbonate. Floor, walls, ceiling, wood-work of the stable should finally be deluged with lime-wash containing chlorinated lime, or formaldehyde solution. The chlorinated lime is cheap and equally effective with the formaldehyde when there is no special objection to its use. From six to eight ounces of the chlorinated lime may be added to each gallon of lime-wash; or the official formaldehyde solution may be used in the proportion of 1:30 to 1:20. Hay, straw, manure, and the general refuse of an infected stable may be burned, or preserved for use as a fertilizer by mixing with chlorinated lime and allowing to stand for some weeks.

*In all cases of disinfection success depends upon the thoroughness with which the process is carried out.*

The following table has been compiled by H. C. Wood, Jr., showing the solutions of various germicides equivalent to a 1:2000 or a 1:10,000 corrosive sublimate solution:

Mercury bichloride ..	1:2000	1:10,000	Creosote .....	1:100
Mercury biniodide ..	1:3000	1:15,000	Sulphuric acid .....	1:100
Silver nitrate .....	1:400	1:4000	Sulphurous acid .....	1:50
Chlorinated lime .....	1:100	1:1000	Sodium hydrate .....	1:100
Formaldehyde .....	1:50	1:150	Solution of chlorinated soda .....	1:50
Lysol .....	1:40	1:150	Phenol sodique .....	1:25
Phenol .....	1:30	1:100	Platt's chlorides .....	1:20
Creolin .....	1:5	1:75	Water of hydrogen dioxide	
Iodine .....		1:500	(U. S. P.) .....	1:3
Salicylic acid .....	1:150		Alcohol .....	1:3
Cupric sulphate .....	1:200		Listerine .....	pure
Thymol .....	1:150		Volatile oils .....	pure
Potassium permanganate .....	1:100		Ichthylol .....	pure



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# APPENDIX.

## APOTHECARIES' WEIGHT—APOTHECARIES' MEASURE.

FORMERLY OFFICIAL IN THE UNITED STATES PHARMACOPŒIA.

Pound,	℔	=	12 Ounces.	Gallon,	C	=	8 Pints.
Ounce,	℥	=	8 Drachms.	Pint,	O	=	16 Fluidounces.
Drachm,	ʒ	=	3 Scruples.	Fluidounce,	℥ss	=	8 Fluidrachms.
Scruple,	ʒ	=	20 Grains.	Fluidrachm,	℥ss	=	60 Minims.
Grain,	gr.	=	1 Grain.	Minim,	℥	=	1 Minim.

## WEIGHTS AND MEASURES OF THE METRIC OR FRENCH SYSTEM.

NOW OFFICIAL IN THE UNITED STATES PHARMACOPŒIA.

### MEASURES OF LENGTH.

One Myriametre	=	10,000 Metres.
One Kilometre	=	1,000 Metres.
One Hectometre	=	100 Metres.
One Decametre	=	10 Metres.
One METRE	=	the ten-millionth part of a quarter of the meridian of the earth.
One Decimetre	=	the tenth part of one Metre or 0.1 Metre.
One Centimetre	=	the hundredth part of one Metre, or 0.01 Metre; written Cm.
One Millimetre	=	the thousandth part of one Metre, or 0.001 Metre; written Mm.

### WEIGHTS.

One Myriagramme	=	10,000 Grammes.
One Kilogramme	=	1,000 Grammes.
One Hectogramme	=	100 Grammes.
One Decagramme	=	10 Grammes.
One GRAMME	=	the weight of a cubic Centimetre of Water at 4° C.; written Gm.
One Decigramme	=	the tenth part of one Gramme, or 0.1 Gramme.
One Centigramme	=	the hundredth part of one Gramme, or 0.01 Gramme.
One Milligramme	=	the thousandth part of one Gramme, or 0.001 Gramme.

### MEASURES OF CAPACITY.

One Myrialitre	=	10 cubic Metres, or the measure of 10 Milliers of Water.
One Kilolitre	=	1 cubic Metre, or the measure of 1 Millier of Water.
One Hectolitre	=	100 cubic Decimetres, or the measure of 1 Quintal of Water.
One Decalitre	=	10 cubic Decimetres, or the measure of 1 Myriagramme of Water.
One LITRE	=	1 cubic Decimetre, or the measure of 1 Kilogramme of Water.
One Decilitre	=	100 cubic Centimetres, or the measure of 1 Hectogramme of Water.
One Centilitre	=	10 cubic Centimetres, or the measure of 1 Decagramme of Water.
One Millitre	=	1 cubic Centimetre, or the measure of 1 Gramme of Water.



# RELATION OF APOTHECARIES' WEIGHTS AND MEASURES TO EACH OTHER.

*In distilled water at the temperature of 60°.*

One Pound	=	0.7900031 Pint	=	6067.2238 Minims.
One Ounce	=	1.0533376 Fluidounces	=	505.6019 Minims.
One Drachm	=	1.0533376 Fluidrachms	=	63.2002 Minims.
One Scruple	=	.....	=	21.0667 Minims.
One Grain	=	.....	=	1.0533 Minims.
One Gallon	=	10.1265427 Pounds	=	58328.8862 Grains.
One Pint	=	1.2658178 Pounds	=	7291.1107 Grains.
One Fluidounce	=	0.9493633 Ounce	=	455.6944 Grains.
One Fluidrachm	=	0.9493633 Drachm	=	56.9618 Grains.
One Minim	=	.....	=	0.9493 Grain.

# RELATION OF APOTHECARIES' OR WINE MEASURE TO CUBIC MEASURE.

One Gallon	=	231.	Cubic Inches.	One Fluidrachm	=	0.22558 Cubic Inch
One Pint	=	28.875	Cubic Inches.	One Minim	=	0.00375 Cubic Inch.
One Fluidounce	=	1.80468	Cubic Inches.			

# RELATION OF APOTHECARIES' WEIGHTS TO METRICAL WEIGHTS.

*Fraction of a grain in*      *Grains in equivalent metrical*      *Drachms, Ounces, and Pounds in*  
*Milligrammes.*      *weights.*      *equivalent metrical weights.*

Grain.	Milligrammes.	Grains.	Centigrammes.	Drachms.	Grammes.
$\frac{1}{48}$	=	1.012	1 = 6.479	1 =	3.887
$\frac{1}{60}$	=	1.079	Decigrammes.	2 =	7.775
$\frac{1}{80}$	=	1.295	2 =		Decagrammes.
$\frac{1}{96}$	=	1.349	3 =	3 =	1.166
$\frac{1}{120}$	=	1.619	4 =	4 =	1.555
$\frac{1}{160}$	=	1.799	5 =	5 =	1.943
$\frac{1}{200}$	=	2.159	6 =	6 =	2.332
$\frac{1}{256}$	=	2.591	7 =	7 =	2.721
$\frac{1}{320}$	=	2.699	8 =	Ounces.	
$\frac{1}{400}$	=	3.239	9 =	1 =	3.1103
$\frac{1}{512}$	=	4.049	10 =	2 =	6.2206
$\frac{1}{640}$	=	4.319	12 =	3 =	9.3309
$\frac{1}{800}$	=	5.399	15 =	4 =	Hectogrammes.
$\frac{1}{1000}$	=	6.479	Grammes.	5 =	1.2441
$\frac{1}{1280}$	=	8.098	16 =	6 =	1.5551
$\frac{1}{1600}$	=	10.798	20 =	7 =	1.8661
$\frac{1}{2000}$	=	12.958	24 =	8 =	2.1772
$\frac{1}{2560}$	=	16.197	25 =	9 =	2.4882
$\frac{1}{3200}$	=	21.597	30 =	10 =	2.7992
$\frac{1}{4000}$	=	32.395	40 =	11 =	3.1103
			50 =	Pounds.	3.4213
			60 =	1 =	7.3724
				2 =	7.4648
				3 =	Kilogrammes.
					1.1197

## RELATION OF METRICAL WEIGHTS TO APOTHECARIES' WEIGHTS.

<i>Metrical Weights.</i>	<i>Exact equivalents in grains.</i>	<i>Approximate equivalents in grains.</i>	<i>Metrical Weights.</i>	<i>Exact equivalents in grains.</i>	<i>Approximate equivalents in Troy Weight.</i>
<b>Milligrammes.</b>			<b>Grammes.</b>		
1 =	.0154	$\frac{1}{65}$	1 =	15.434	gr. xv.
2 =	.0308	$\frac{1}{32}$	2 =	30.868	3ss.
3 =	.0463	$\frac{1}{21}$	3 =	46.302	3ij.
4 =	.0617	$\frac{1}{16}$	4 =	61.736	5i.
5 =	.0771	$\frac{1}{13}$	5 =	77.170	3iv.
6 =	.0926	$\frac{1}{11}$	6 =	92.604	5iss.
7 =	.1080	$\frac{1}{9}$	7 =	108.038	3vss.
8 =	.1234	$\frac{1}{8}$	8 =	123.472	5ij.
9 =	.1389	$\frac{1}{7}$	9 =	138.906	3vij.
<b>Centigrammes.</b>			<b>Decagrammes</b>		
1 =	.1543	$\frac{1}{65}$	1 =	154.340	5iiss.
2 =	.3086	$\frac{1}{32}$	2 =	308.680	3v.
3 =	.4630	$\frac{6}{13}$	3 =	463.020	3viiss.
4 =	.6173	$\frac{7}{11}$	4 =	617.360	3x.
5 =	.7717	$\frac{3}{4}$	5 =	771.701	3xij.
6 =	.9260	$\frac{8}{10}$	6 =	926.041	3xv.
7 =	1.0803	1	7 =	1,080.381	3xvii.
8 =	1.2347	$1\frac{1}{4}$	8 =	1,234.721	3xx.
9 =	1.3890	$1\frac{1}{3}$	9 =	1,389.062	3xxij.
<b>Decigrammes.</b>			<b>Hectogrammes.</b>		
1 =	1.543	$1\frac{1}{2}$	1 =	1,543.402	3iii 3v.
2 =	3.086	3	2 =	3,086.804	3vj 3iij.
3 =	4.630	$4\frac{1}{2}$	3 =	4,630.206	3ix 3v.
4 =	6.173	6	4 =	6,173.609	3bi 3vij.
5 =	7.717	$7\frac{1}{2}$	5 =	7,717.011	3bi 3iv.
6 =	9.260	9	6 =	9,260.413	3bi 3vij.
7 =	10.803	11	7 =	10,803.816	3bi 3x 3iv.
8 =	12.347	$12\frac{1}{2}$	8 =	12,347.218	3bij 3i 3v.
9 =	13.890	14	9 =	13,890.620	3bij 3v.
			<b>Kilogramme.</b>		
			1 =	15,434.574	3bij. 3viiij.
			<b>Myriagramme.</b>		
			1 =	154,340.23	{ 3lb xxvi. 3ix 3iv.

TABLE OF THE PROPORTION BY MEASURE OF ALCOHOL (SP. GR. 0.825) CONTAINED IN ONE HUNDRED PARTS OF DIFFERENT WINES, ETC.\*

Lisa (mean).....	25.41	Teneriffe.....	19.79	Lunel.....	15.52
Raisin wine (mean)....	25.12	Teneriffe (C.).....	16.61	Ditto (F.).....	18.10
Marsala [Sicily ma- deira] (mean)....	25.09	Colares.....	19.75	Shiraz.....	15.52
strongest (J.).....	21.10	Lachryma Christi.....	19.70	Ditto (C.).....	15.56
weakest (J.).....	19.90	White Constantia.....	19.75	Syracuse.....	15.28
Port, strongest.....	25.83	Red Constantia.....	18.92	Sauterne.....	14.22
mean.....	22.96	Lisbon.....	18.94	Burgundy (mean)....	14.57
weakest.....	19.00	Ditto (C.).....	19.09	strongest (J.).....	13.20
strongest (C.).....	20.49	Bucellas.....	18.49	weakest (J.).....	10.10
mean (C.).....	18.68	Red madeira (mean)...	20.35	Hock (mean).....	12.08
weakest (C.).....	16.80	Cape muscat.....	18.25	strongest (J.).....	13.00
strongest (J.).....	23.20	Cape madeira (mean) ..	20.51	weakest (J.).....	9.50
weakest (J.).....	20.70	Grape wine.....	18.11	Nice.....	14.63
White port (C.).....	17.22	Calcavella (mean)....	18.65	Barsac.....	13.86
Madeira, strongest.....	24.42	Vidonia.....	19.25	Tont.....	13.30
mean.....	22.27	Alba flora.....	17.26	Champagne (mean)...	12.61
weakest.....	19.24	Zante.....	17.05	Ditto (F.).....	12.20
strongest (C.).....	20.35	Malaga.....	17.26	Ditto, strongest (J.) ..	14.80
strongest (J.).....	19.70	White Hermitage.....	17.43	weakest (J.).....	14.10
weakest (J.).....	19.00	Roussillon (mean)....	18.13	Red hermitage.....	12.32
Sercial madeira.....	21.40	Claret (strongest) .....	17.11	Vin de Grave (mean) ..	13.37
Ditto (C.).....	18.50	mean.....	15.10	Frontignac (Rives Altes).....	12.79
Sherry, strongest.....	19.81	weakest.....	12.91	Ditto (C.).....	12.29
mean.....	19.17	ditto (F.).....	14.73	Côte rôtie.....	12.32
weakest.....	18.25	vin-ordinaire (C.) ..	10.42	Tokay.....	9.88
strongest (C.).....	19.31	Château-Latour, 1825 (C.).....	9.38	Rudesheimer, first quality (C.).....	10.14
mean (C.).....	18.47	first-growth, 1811 (C.).....	9.32	inferior (C.).....	8.35
weakest (C.).....	16.96	strongest (J.).....	11.10	Hambacher, first quality (C.).....	8.88
Amontillado (C.) ..	15.18	weakest (J.).....	9.10	Catawba (Stearns) ..	8 to 11
strongest (J.).....	24.70	Malmsey madeira.....	16.40		
weakest (J.).....	15.40	Ditto (C.).....	15.60		

Cider, highest average .	9.87	Ale (Edinburgh).....	6.20	Brandy.....	53.39
lowest average ....	5.21	Ale (Dorchester).....	5.56	Rum.....	53.68
Perry, average of four samples.....	7.26	Brown stout.....	6.80	Gin.....	51.60
Mead.....	7.32	London porter.....	4.20	Scotch whisky.....	54.32
Ale (Burton).....	8.88	London small beer....	1.28	Irish whisky.....	53.90

\* The analyses whose results are given in this table were mostly made by Mr. Brande. When no mark is attached, the quotation is upon his authority. When the mark (F.) is added, the analysis was made by Julia-Fontenelle; (C.), by Professor Christosn; (J.), by Dr. H. Bence Jones.





## INDEX OF DISEASES

### Abscess :

*alcohol*, to support system by its food value, also as heart stimulant, 204.  
*bismuth oxyiodogallate*, glycerin solution injected into cold abscesses, 307.  
*boric acid*, a feeble antiseptic, 698.  
*formaldehyde*, employed in tuberculous cases, 689.  
*hydrogen dioxide*, as a disinfectant and cleansing agent, 662.  
*iodoform*, in tuberculous forms, 384.  
*menthol*, a saturated alcoholic solution painted on superficial abscesses, 682.  
*opsonic treatment*, 415.  
*papain*, to destroy surrounding membranes in old abscesses, 651.  
*potassium permanganate*, as a cleansing disinfectant when fetid discharges, 660.  
*tannic acid*, when excessive secretion, 286.

### Acidity of Stomach :

*ammonia*, stimulant, promptly acting, too irritating to be used in inflammatory conditions, 186.  
*magnesia*, antacid and gently laxative, 635.  
*soda*, the most generally serviceable antacid, 634.

### Acne :

*arsenic*, valuable alterative, especially in chronic cases, 351.  
*calcium sulphide*, credited with peculiar alterative action, 694.  
*ichthyol*, supposed to possess the power of penetrating the skin and exercising a local alterative action, 396.  
*iodine*, powerfully antiseptic but of doubtful value, 378.  
*oil of cajuput*, stimulant and parasiticide, 442.  
*opsonic treatment*, 415.  
*phosphorus*, used internally in cases with poor nutrition, 340.  
*solution of mercuric nitrate*, caustic, used to destroy pustules, 614.

### Aconite Poisoning :

*alcohol*, a rapidly acting cardiac stimulant, 204.  
*digitalis*, a powerful stimulant to the heart, but slowly acting, 231.  
*Treatment of*, 275.

### Actinomycosis :

*potassium iodide*, only drug likely to be of service internally, 377.

### Addison's Disease :

*suprarenal capsule*, supplies lacking secretions, use must be continued indefinitely, 245.

### Ague :

See MALARIA.

### Alcoholism :

*apomorphine*, emetic and sedative, 495.  
*capsicum*, for alcoholic gastritis, 483.  
*gold and sodium chloride*, supposed to exercise a specific effect on central nervous system in alcoholic habit, but probably valueless, 373.  
*strychnine*, valuable in chronic alcoholism, 140.  
*treatment of acute alcoholism*, 208.  
See also DELIRIUM TREMENS.

### Alopecia :

*arsenic*, in atrophic variety, 351.  
*pilocarpine*, 567.

**Amaurosis :**

See BLINDNESS.

**Amblyopia :**

*strychnine*, especially useful in tobacco or alcoholic cases, 138.

**Amenorrhœa :**

*aloes*, cathartic, tends to increase pelvic congestion, enters into several emmenagogue combinations, 506.

*apiol*, to be given for a week previous to expected menses, 580.

*clove tea*, useful where menses are suppressed by "cold," 481.

*cotton root*, stimulant to uterus, 598.

*diaphoretics*, of service in acute suppressions, 561.

*emmenagogues*, their limitations and uses, 579

*ginger*, may be given in form of infusion, 482.

*oxalic acid*, active but somewhat dangerous, 686.

*potassium permanganate*, not very valuable, but sometimes of service, 581.

*santonin*, has been recommended in acute menstrual suppression, 640.

*sumbul*, useful in cases associated with nervous symptoms, 17.

*turpentine*, when there is much relaxation, 551.

**Ammonia Poisoning :**

*treatment*, 282.

**Ammoniacal Urine :**

See CYSTITIS.

**Anchylostomiasis :**

See UNCINARIASIS.

**Anæmia :**

See CHLOROSIS and PERNICIOUS ANÆMIA.

**Anæsthesia, Accidents in :**

*ammonia*, rapidly acting heart stimulant, 185.

*artificial respiration*, a most important factor, 48.

*cardiac massage*, may be tried in desperate cases, 46.

*treatment of*, 46.

**Aneurism :**

*digitalis*, useful where heart is very feeble, but must be employed with great caution on account of danger of rupture, 229.

*gelatin*, promotes coagulation of the blood, 401.

*potassium iodide*, largely employed, but there is no explanation of the manner in which it benefits, 377.

**Angina :**

See SORE THROAT.

**Angina Pectoris :**

*amyl nitrite*, very prompt and efficacious, to be used during the attack, 168.

*erythrol tetranitrate*, acts like nitroglycerin but more lasting, 170.

**Anorexia :**

*bitters*, stimulate the flow of gastric juice, also probably increase appetite through their bitter taste, 475.

*orexine*, a synthetic bitter, highly lauded, 478.

*quinine*, acts as a bitter, but also has effect on metabolism, 429.

*strychnine*, 138.

**Anthrax :**

*phenol*, to be injected into the ulcer, 669.

**Aortic Lesions :**

See ENDOCARDITIS.



**Aphthous Stomatitis :**

See STOMATITIS.

**Apoplexy :**

*croton oil*, useful as a purgative where patient cannot swallow; also acts as revulsant, 522.  
*emetics*, not useful in true apoplexy, but in those forms of coma resembling apoplexy, 487.  
*nitro-glycerin*, useful to avert threatened apoplexy by dilating the blood-vessels, 169.

**Arsenic Poisoning :**

*ferric hydroxide*, this, the best chemical antidote, may be prepared extemporaneously by adding any alkali to a solution of ferric sulphate or chloride, 328.  
*treatment*, 355.

**Arteriosclerosis :**

*digitalis*, if heart is weak, 229.  
*nitrites*, to lower pressure by dilating blood-vessels, 169.

**Ascites :**

See DROPSY.

**Asthenopia :**

*strychnine*, acts almost specifically, 139.

**Asthma :**

*Symptomatic Treatment:*

*amyl nitrite*, very prompt and powerful, used by inhalation during attack, 169.  
*anæsthetics*, sometimes useful during attack, 22.  
*atropine*, may be given hypodermically in large doses, probably less useful than the burning belladonna, 104.  
*belladonna*, useful, especially to be burned and vapors inhaled, 104.  
*chloral*, occasionally but not generally useful, 80.  
*chloralformamid*, recommended in asthma depending upon cardiac disease, 90.  
*compound arsenical paper formula* for a compound to be smoked, (note) 572.  
*emetics*, 487.  
*dionine*, 73.  
*gelsemium*, 173.  
*grindelia*, useful as an expectorant, may be added to a burning powder, 576.  
*heroin*, especially useful in secondary asthma, acts by lessening irritability of respiratory centers, 75.  
*lobelia*, may be used as an expectorant, also in emetic doses during paroxysms, 171.  
*nitroglycerin*, may be used hypodermically in the place of amyl nitrite.

*Constitutional Treatment:*

*antipyrine*, lessens irritability of nervous system, 463.  
*arsenic*, may be used either locally or internally, 351.  
*aspidosperma*, acts upon respiratory center, 178.  
*atropine*, may be used as a preventative of spasmodic asthma, 104.  
*hyoscine*, similar to atropine in its effect, more sedative, 111.  
*potassium iodide*, one of the most valuable drugs known between the paroxysms, 376.  
*pyramidon*, 472.  
*spartein*, may be employed in asthma depending upon cardiac lesions, 250.  
*suprarenal capsules*, recommended to be used internally, 246.

**Atropine Poisoning :**

*pilocarpine*, physiological antagonist to atropine, 568.  
*treatment of*, 108.

**Belladonna Poisoning :**

See ATROPINE POISONING.

**Biliousness :**

- emetics*, mechanically relieve portal congestions, 487.
- ipecacuanha*, has a special action on the liver, 491.
- mercury*, in the form of calomel or blue-mass, the most generally valuable remedy in acute cases, 515.
- nitro-hydrochloric acid*, of service especially in chronic cases, 333.
- oxgall*, is the most powerful stimulant to hepatic secretion known, 508.
- podophyllum*, sometimes called "vegetable mercury" on account of its effect on the liver, 518.
- potassium acetate* and *citrate*, of service in chronic biliousness, 538.

**Bites :**

See HYDROPHOBIA, also SNAKE-BITES.

**Black-water Fever :**

*methylene-blue*, is destructive to malarial parasite, but not irritant to the kidney, 439.

**Bladder, Irritable :**

See CYSTITIS.

**Blindness :**

- santonin*, 640.
- strychnine*, especially useful in toxic cases as alcohol or tobacco, 138.

**Boils :**

- calcium sulphide*, useful where successive crops of boils, 694.
- infiltration anæsthesia*, to open boils, 53.
- menthol*, saturated alcoholic solution painted over area will sometimes abort, 682.
- opsonic treatment*, 415.
- phosphorus*, as general tonic and alterative, 340.

**Bone Diseases :**

- iodine*, internally in scrofulous cases, 376.
- phenol*, injected deeply, 669.
- phosphorus*, has a stimulant action on growth of bone, 340.

**Brain Softening :**

*phosphorus*, sometimes of benefit, 340.

**Bright's Disease :**

- antipyrine*, 464.
- apocynum*, to eliminate dropsical effusions, 237.
- caffeine*, to evacuate dropsy, to be used only very cautiously if at all in acute cases, 217.
- calomel*, one of the most powerful diuretics known, 530.
- diaphoretics*, aid in the excretion of waste products through the skin, 562.
- gallic acid*, to diminish excessive secretion in chronic interstitial nephritis, 287.
- hypodermoclysis*, in acute irritation of kidneys or suppression, 526.
- pilocarpine*, may be used to produce sweating, also to stimulate kidney in acute suppression, 567.
- potassium bitartrate*, of value in acute nephritis, 539.
- strontium lactate*, claimed to diminish the amount of albumin, but of doubtful value, 545.
- strophanthus*, more stimulant to kidneys than *digitalis*, 241.
- tannalbin*, in cases where large amounts of albumin, 289.
- theobromine*, may be employed in both acute and chronic cases when secretion is insufficient, 532.
- theocin*, a synthetic alkaloid of value in dropsical cases, 532.
- thyroid extract*, 496.
- tincture of ferric chloride*, much employed in chronic cases, 328.
- water*, in acute irritations large draughts of water often valuable, 526.

**Bronchitis, Acute :**

- ammonium chloride*, somewhat stimulant, use after secretion is established, 185.
- antimony*, to be employed only in robust or sthenic patients, 260.
- apomorphine hydrochloride*, encourages the establishment of secretion, 495.

**Bronchitis, Acute (Continued):**

- codeine*, as a cough sedative, 72.
- demulcents*, 617.
- eucalyptus*, used when there is free secretion, 442.
- heroin*, a very valuable cough sedative, 75.
- ipecaacuanha*, increases expectoration, use in early stages, 573.
- licorice*, 619.
- lobelia*, of service when there is tendency to asthmatic spasms, 171.
- oil of sandal-wood*, in the latter stages, 555.
- opium*, cough sedative, avoid where expectoration is profuse, 65.
- potassium citrate*, increases secretion, especially serviceable in early stages, 573.
- senega*, 574.
- steam atomizer*, method of using, 572.
- sulphuretted hydrogen*, useful where free expectoration, 578.
- tar*, used only in advanced stages, 576.
- terebene*, stimulating expectorant, use in later stages, 575.
- terpin hydrate*, of service after secretion has been established, 575.
- turpentine stupes*, act by counter-irritation, 550.

**Bronchitis, Chronic:**

- ammoniac*, 577.
- ammonium chloride*, employed where expectoration is not profuse, 185.
- arsenic*, may be used either internally or in form of cigarettes, 351.
- asa fetida*, of service in the aged, 17.
- aspidosperma*, to relieve dyspnoea, 180.
- balsam of Tolu*, 577.
- benzoic acid*, a valuable remedy, 692.
- Burgundy pitch*, externally as a counter-irritant, 610.
- cimicifuga*, 19.
- copaiba*, in cases with free muco-purulent expectoration, 553.
- creosote*, one of the most active stimulating expectorants, 675.
- creosote carbonate*, supposed to be less irritating to the stomach than creosote, 670.
- eucalyptus*, an active stimulant expectorant, 442.
- formaldehyde*, inhalations of, 689.
- grindelia*, relaxes spasm of bronchial muscles and stimulates mucous membranes, 576.
- naphthalin*, when free expectoration, 680.
- oil of sandal-wood*, a useful stimulant expectorant, 555.
- oil of turpentine*, 551.
- physostigma*, when there is weakness of bronchial muscles, 151.
- strychnine*, as a stimulant in the feeble to aid expulsion of secretion, 139.
- sulphuretted hydrogen*, an unpleasant but active remedy especially where purulent expectoration, 578.
- tar*, a useful remedy best employed in form of syrup, 576.
- terbene*, an active stimulating expectorant, 575.
- terpin hydrate*, a very useful drug in cases of mild type, 575.
- theocol*, 678.

**Bronchorrhœa:**

- atomization*, as a means of applying remedies locally, 572.
- gallic acid*, an internal astringent, 287.

**Bruises:**

- arnica*, 610.
- camphor*, 191.
- ichthyol*, 396.
- solution of lead subacetate*, sedative and astringent embrocation, 294.
- vinegar*, a useful external application, 290.

**Buboes:**

- chloral*, in solution forms a stimulant and antiseptic wash, 80.
- phenol*, deep injections of, 669.

**Bubonic Plague:**

- serum treatment*, useful as prophylactic as well as curative, 412.



**Burns :**

- aluminum hydroxide*, mildly astringent and protective, 292.
- boric acid*, as a mildly antiseptic dressing, 698.
- Carron oil*, a soothing local application, 637.
- chalk*, offers a desiccant protective dusting powder, 637.
- creosote*, recommended when there is excessive granulation, 676.
- hot baths*, to combat the collapse, 560.
- ichthyol*, 396.
- iodoform*, analgesic, desiccant, and antiseptic, 382.
- lead carbonate*, in the form of ointment is a sedative astringent, use with care, 294.
- orthoform*, local anæsthetic and antiseptic, 52.
- phenol*, anæsthetic and germicidal, 669.
- treatment of*, (note) 382.
- volatile oils*, (note) 479.

**Bursitis :**

- phenol*, deeply injected, 669

**Cachexia :**

- cod-liver oil*, appears to have specific influence on nutrition, 390.
- glycerin*, 626.

**Calculi :**

- anæsthetics*, to alleviate pain and produce relaxation during passage of stone, 22.
- atropine*, to relieve spasm, 104.
- benzoic acid*, in uric acid calculi, supposed to check elimination of uric acid, 692.
- olive oil*, probably of some value in cholelithiasis, 622.
- piperazine*, will not dissolve calculi, 543.
- potassium acetate*, to check the further deposition of uric acid, 538.
- sodium salts*, to lessen viscosity of bile in gall-stones, 634.

**Cancer :**

- arsenic*, as a caustic in inoperable cases, 613.
- chloral*, locally anæsthetic and antiseptic, 80.
- cocaine*, to relieve pain, apply locally, 126.
- escharotics*, only to be used in inoperable cases, 611.
- formaldehyde*, deodorant and germicidal, 689.
- iodoform*, lessens pain and absorbs discharge, 382.
- methylene blue*, 439.
- solution of mercuric nitrate*, as a caustic, 614.

**Cancer of Stomach :**

- bismuth subnitrate*, to relieve pain and vomiting, 306.
- chlortone*, local anæsthetic, 92.
- diastase*, to digest food when gastric secretions fail, 650.
- malt*, 650.

**Carbolic Acid Poisoning :**

- treatment*, 672.

**Carbuncle :**

- menthol*, paint saturated alcoholic solution over surface 682.
- opsonic treatment*, 415.

**Cardiac Disease, Chronic :**

- See HEART DISEASE.

**Cardiac Dropsy :**

- See DROPSY.

**Cardialgia :**

- antacids*, correct hyperacidity, 631.
- charcoal*, to absorb gases, 652.

**Cataract :**

- phosphorus*, 340.

**Catarrh of Air Passages :**

*bismuth subnitrate*, sedative astringent for local application in acute cases, 306.  
*benzoic acid*, to be given internally in subacute and chronic cases, 692.  
*camphoric acid*, applied locally, 192.  
*flaxseed*, may be used freely in the form of a decoction, 619.  
*guaiacol*, as a stimulant in chronic cases, 677.  
*hydrastin*, applied locally, 595.  
*thymol iodide*, dusted on the mucous membranes, 387.  
 See also *Bronchitis* and *Coryza*.

**Catarrh of Bladder :**

See CYSTITIS.

**Catarrhal Jaundice :**

See JAUNDICE.

**Cerebral Congestion :**

*cathartics*, 500.  
*ergot*, 589.

**Cerebral Excitement :**

*cathartics*, act by revulsion, 500.  
*potassium bromide*, useful when condition is not inflammatory, 156.

**Cerebral Softening :**

See BRAIN SOFTENING.

**Chancres and Chancroids :**

*black wash*, as a local application, 370.  
*Canquoin's paste*, contains zinc chloride, 614.  
*corrosive sublimate*, less useful than solution of mercuric nitrate but actively germicidal and somewhat caustic, 614.  
*escharotics*, 611.  
*hydrogen dioxide*, cleansing and germicidal, 662.  
*nitric acid*, should be applied with a glass rod, 332, 615.  
*red mercuric oxide*, may be used in powder form, 370.  
*resorcin*, apply as dusting powder, 685.  
*solution of mercuric nitrate*, actively caustic, 614.  
*sulphuric acid*, actively caustic, 330.  
*yellow wash*, 370.

**Chapped Hands, Lips, or Nipples :**

*benzoic acid*, stimulant and antiseptic, especially useful in the form of benzoin, 693.  
*glycerin*, 626.  
*tannic acid*, to harden tender nipples, 286.

**Chilblains :**

*copaiba*, 553.  
*creosote*, 676.

**Child-birth :**

See LABOR.

**Chloral Poisoning :**

*treatment of*, 82.

**Chlorosis :**

*bone marrow*, 531.  
*cacodylic acid*, doubtful if it is of value, 359.  
*ceptrin*, 620.  
*copper sulphate*, an old remedy, recently revived in cases with amenorrhœa, 310.  
*euquinine*, 436.  
*iron*, almost a specific, 326.  
*lecin*, probably of some value but less beneficial than iron, 399.

**Cholelithiasis :**

See CALCULI.

**Cholera Asiatica :**

- acetozone*, an active intestinal antiseptic, 663.
- ammonia*, for the collapse, 185.
- antitoxin*, especially for immunization, 411.
- camphor*, to lessen the diarrhoea, 191.
- sulphuric acid*, of value as a prophylactic, 330.

**Cholera Infantum :**

- antipyrine*, 464.
- bismuth subnitrate*, one of the most useful remedies known, 306.
- creosote*, of service on account of local anæsthetic as well as antiseptic action, 675.
- resorcinol*, antiseptic, 684.
- rhubarb*, purgative and astringent, 504.
- sodium phosphate*, useful to clean out bowel and encourage flow of bile, 511.
- sulphuric acid*, actively astringent, 330.

**Chordee :**

- camphor*, 191.
- sulphonol*, asserted to act as a sexual sedative, 84.

**Chorea :**

- antipyrine*, has some effect as motor sedative, 462.
- apomorphine*, has been recommended in acute cases, 495.
- arsenic*, one of the most generally useful remedies, give Fowler's solution in increasing doses, 352.
- cacodylic acid*, an arsenical preparation, 359.
- Calabar bean*, 151.
- chloral*, to temporarily control convulsions when violent, 79.
- cinicifuga*, give in conjunction with iron, 19.
- conium*, 178.
- euquinine*, used like quinine, 436.
- quinine*, efficacious when patient can take large enough quantities, stimulates spinal inhibitory center, 429.
- strychnine*, if any value it is as general tonic, 138.
- sulphonol*, 84.
- zinc oxide*, 309.

**Chronic Intestinal Atony :**

- Calabar bean*, a stimulant to non-striated muscle fibre, 151.

**Chyluria :**

- methylene-blue*, 439.

**Cicatrices :**

- thiosinamine*, asserted to have the power of absorbing scar tissue, 398.

**Cirrhosis of the Liver :**

- apocynum*, to evacuate effusion, 237.
- nitro-hydrochloric acid*, in early stages exercises a directly beneficial action on liver, 333.
- See also DROPSY.

**Cocaine-poisoning :**

- treatment of*, 127.

**Cocainism :**

- treatment of*, 129.

**Colchicum-poisoning :**

- treatment of*, 395.

**Cold, a General :**

- alcohol*, as a preventive, 206.
- diaphoretics*, most efficacious treatment, 561.
- licorice*, 619.
- See also BRONCHITIS and CORYZA.



**Colic :**

*antacids*, in conditions with hyperacidity, 631.  
*asafoetida*, in flatulent colic, a useful stimulant to peristalsis, 17.  
*atropine*, useful in spasmodic colic, 104.  
*cajuput*, 442.  
*chloroform*, anodyne and carminative, frequently very useful, 34.  
*ether*, mildly carminative, 29.  
*ginger*, actively carminative, useful in flatulent colic, 482.  
*opium*, to allay irritation, 65.

**Colica Pictorum :**

*alum*, chemical antidote to lead, also claimed to act specifically, 292.  
*belladonna*, probably most useful drug in this condition, 104.  
 See also LEAD-POISONING.

**Colitis :**

*castor oil*, purgative and sedative to inflamed mucous membrane, 522.  
*copper sulphate*, occasionally useful, applied locally, 310.  
*high enemata*, best treatment; various drugs, as silver nitrate or potassium chlorate, may be thus locally applied, 501.  
*magnesium sulphate*, benefits by cleaning out the cause, 510.  
*silver nitrate*, probably the most generally useful local application, 317.

**Collapse :**

*ammonia*, prompt but temporary heart stimulant, give hypodermically, 185.  
*atropine*, vaso-motor stimulant, especially useful in cases with subnormal temperature, 105.  
*caffeine*, sodium and caffeine benzoate for hypodermic use, 217.  
*counter-irritants*, 603.  
*digitalis*, powerful but slow, may be given hypodermically, 230.  
*ergot*, slow in its effect, 589.  
*ether*, 30.  
*hot baths*, only efficient method of maintaining body temperature, 560.  
*hypodermoclysis*, of physiological salt solution one of most efficient means of maintaining the circulation, 526.  
*sodium carbonate*, 634.  
*suprarenal extract*, very quick but fugacious, may be given intravenously, but a dangerous remedy, 245.  
*Warburg's tincture*, 436.

**Colliquative Sweats :**

See NIGHT-SWEATS.

**Coma :**

*emetics*, 487.

**Comedo :**

*arsenic*, 351.

**Condylomata :**

*chromic acid*, caustic, 615.  
*nitric acid*, actively caustic, 615.  
*phenol*, mildly caustic, 669.

**Congestion of Brain :**

See CEREBRAL CONGESTION.

**Congestion of Lungs :**

*atropine*, 104.  
*ergot*, 589.

**Congestion of Spinal Cord :**

*ergot*, 589.

**Conium-poisoning :**

*treatment of*, 179

**Conjunctivitis :**

- alum*, in the form of alum curd, astringent, 292.
- betanaphthol*, applied locally dissolved in olive oil, 681.
- boric acid*, one of the best local applications, soothing and antiseptic, 698.
- citric ointment*, in chronic cases, 371.
- copper sulphate*, used in the granular type, 310.
- ichthargan*, may be topically applied in one per cent. solution, 320.
- largin*, a modern silver preparation recommended in the form of gelatin tablets locally, 319.
- lithium*, in gouty cases, 543.
- protargol*, recommended especially in gonorrhœal cases, 321.
- silver nitrate*, a standard and useful treatment, an active germicide and astringent, 316.
- suparenal extract*, powerfully antagonizes the congestion, 245.
- yellow mercuric oxide*, in chronic cases 371.

**Constipation :**

- aloes*, in atonic cases, especially when accompanied with amenorrhœa, 506.
- asafetida*, as stimulant to the intestinal muscles, especially useful in the aged, 17.
- atropine*, in cases due to spasmodic constriction of the bowel, 104.
- belladonna*, prevents griping and increases laxative effects of cathartics, 104.
- calomel*, most valuable drug in biliousness, not to be used habitually, 515.
- cascara sagrada*, especially useful in chronic constipation, 507.
- castor oil*, useful only in acute cases, 521.
- cathartics*, 498.
- croton oil*, probably most powerful purgative known used to revulse or when patients refuse to swallow, 522.
- diet*, 502.
- enemata*, 500.
- Epsom salt*, a prompt and efficient saline, 510.
- euonymus*, 520.
- magnesia*, antacid laxative, 635.
- manna*, 503.
- physostigma*, stimulant to intestinal muscles, useful in atonic cases, 151.
- podophyllum*, supposed to act upon the liver, hence the name "vegetable mercury," 518.
- rhubarb*, used in debilitated cases, 504.
- senna*, a very efficient laxative when soft passages desired, 506.
- solution of magnesium citrate*, useful on account of its agreeable flavor, 513.
- strychnine*, when intestinal atony, 139.
- sulphur*, 694.
- tamarind*, a laxative fruit, 503.
- treatment of*, 498.
- wahoo*, in chronic cases with hepatic torpor, 520.

**Convulsions :**

- amyl nitrite*, the remedy when convulsions must be controlled immediately, quick and powerful but fugacious, 168.
- anæsthetics*, when prompt action desired; chloroform the most efficacious, 22.
- asafetida*, in hysterical cases, 17.
- camphor*, of little value except in hysteria, 191.
- chloral hydrate*, useful in all types of convulsions if severe enough to threaten life, 80.
- emetics*, when convulsions of gastric origin, 487.
- musk*, 15.
- bromides*, useful when a persistent action desired, 157.
- See also EPILEPSY, TETANUS, etc.

**Copper-poisoning :**

- treatment of*, 311.

**Corneal Ulcer :**

- atropine*, rests the eye by paralyzing accommodation, 106.
- dionine*, increases the lymphatic circulation in the eye, 74.
- largin*, germicidal, 319.
- physostigmine*, to limit the spread of ulcers, 152.

**Corpulence :**

See OBESITY.

**Corrosive Sublimate poisoning :**

*treatment of*, 372.

**Coryza :**

*atropine*, give internally in acute stage; it checks excessive secretion, 105.  
*bismuth subnitrate*, locally applied, soothing and protective, 306.  
*cocaine*, contracts the engorged vessels, 126.  
*cubebs*, as a snuff in not too acute conditions, 554.  
*glycerin*, locally, 626.  
*ichthyol*, a ten per cent. ointment locally, 396.  
*salipyrin*, 472.

**Cough :**

*atropine*, when cough is of spasmodic character, 104.  
*codeine*, acts on respiratory center, 72.  
*dionine*, 73.  
*gelsemium*, when of nervous type, 173.  
*heroine*, one of most generally useful cough sedatives known, 75.  
*opium*, to be avoided when expectoration is profuse, 65.  
*prussic acid*, of little value, 280.  
*treatment of*, 570.

**Cretinism :**

*thyroid extract*, 405.

**Croup :**

*emetics*, to evacuate membrane or mucus, 487.  
*expectorants*, 571.  
*glycerin*, 626.  
*ipecacuanha*, emetic and expectorant, 491.  
*lime-water*, apply locally by means of an atomizer 637.

**Cystitis :**

*arbutin*, alterative diuretic, 547.  
*benzoic acid*, valuable urinary antiseptic, especially useful when ammoniacal urine, 693.  
*benzosulphinide*, as a urinary antiseptic, 627.  
*betol*, antiseptic, 681.  
*boric acid*, antiseptic, may be given by mouth or used to wash out bladder, 698.  
*buchu*, acts as sedative to inflamed mucous membrane, 546  
*camphoric acid*, 192.  
*copaiba*, in chronic cases, 553.  
*flaxseed*, infusion, sedative to mucous membrane, useful in acute cases, 619.  
*grindelia*, 577.  
*guaiacol*, urinary antiseptic, 677.  
*hexamethylenamine*, one of the best urinary disinfectants, supposed to liberate formaldehyde in the bladder, 557.  
*hippurate of lime and lithia*, (note) 691.  
*iodine*, 378.  
*juniper*, in chronic cases, 555.  
*methylene-blue*, mildly antiseptic, 439.  
*pareira*, 547.  
*resorcinol*, a three per cent. solution employed to irrigate the bladder, 685.  
*salicylic acid*, rarely used to-day, 452.  
*silver citrate*, as local application to bladder 319.  
*terebene*, stimulant alterative diuretic, 575.  
*terpin hydrate*, 575.  
*tritium*, sedative to cystic mucous membrane, 548.  
*turpentine*, in chronic cases, 551.  
*uva ursi*, a valuable sedative alterative diuretic, 547.  
*water*, dilutes irritating urine, 526.



**Debility :**

See NEURASTHENIA.

**Delirium of Low Fevers :**

*blisters*, when condition is not due to exhaustion, 603.

*chloral*, in early stages, 79.

*valerian*, 16.

**Delirium Tremens :**

*chloral*, to produce sleep, powerful but depressant, 79.

*chloretone*, a very uncertain hypnotic, 92.

*digitalis*, to maintain circulation, large doses well borne, 230.

*hops*, 18.

*hyoscine hydrobromide*, a useful hypnotic, especially in combination with morphine, 110.

*monobromated camphor*, of little value, 161.

*opium*, serviceable, but not to be used too lavishly, 64.

*paraldehyde*, a useful somnifacient, 88.

*potassium bromide*, as a general nerve sedative, not to produce sleep, 157.

*valerian*, too feeble, 16.

**Dermatitis :**

*vinegar*, a soothing astringent lotion, 290.

**Diabetes Insipidus :**

*antipyrine*, 464.

*ergot*, probably the most generally useful remedy known, 589.

*opium*, may be used in combination with gallic acid, 65.

**Diabetes Mellitus :**

*antipyrine*, 464.

*arsenical solution of lithium*, in gouty cases, (note) 543.

*ergot*, may do good, usually fails, 589.

*eucalyptus*, 442.

*glycerin*, as a sweetening agent instead of sugar, 626.

*hydrogen dioxide*, probably of no service, 662.

*jambul*, in some cases may greatly reduce sugar, usually no effect, 398.

*lecithin*, recommended to improve nutrition, 399.

*opium*, the most valuable drug in this condition, use in large doses, 65.

*piperazine*, recommended on scientific grounds, (note) 544.

*saccharin*, extraordinarily sweet, used as substitute for sugar, 627.

*salicylic acid*, has been highly commended, 452.

*sodium carbonate*, 634.

**Diarrhœa :**

*antacids*, in cases with "spinach-stools," 631.

*antipyrin*, 464.

*argemone*, as an astringent antiseptic, 319.

*aromatics*, in diarrhœas of relaxation, 479.

*astringents*, 284.

*atropine*, in colliquative diarrhœas, 105.

*bismuth and ammonium citrate*, differs essentially from other salts of bismuth, useful only in serous types, 307.

*bismuth*, the insoluble salts of bismuth are the most generally valuable remedies we have in diarrhœas of an inflammatory character, their action is sedative, protective antiseptic and astringent, 306.

*calcium carbonate*, in summer diarrhœas when intestines are acid, 637.

*camphor*, in serous forms of diarrhœa, 191.

*castor oil*, useful to cleanse bowel in inflammatory diarrhœa, is sedative, 521.

*cocaine*, 126.

*copaiba*, in chronic cases, 553.

*copper sulphate*, used in chronic ulcerative types, but is of little value, 310.

*creosote*, intestinal antiseptic 675.

*cresol*, antiseptic, 679.

*ergot*, in chronic serous diarrhœas restores tone to relaxed vessels, a valuable remedy, 588.

**Diarrhœa (Continued):**

- hæmatoxylin*, efficient astringent with pleasant taste, 288.  
*Hope's camphor mixture*, a valuable combination in serous diarrhœas, 332.  
*ipeacuanha*, in chronic cases, 491.  
*jambul*, 398.  
*lead acetate*, employed in serous diarrhœas combined with opium, 294.  
*magnesia*, in cases with intestinal acidity, 635.  
*naphtol*, a valuable intestinal antiseptic, 681.  
*nitro-hydrochloric acid*, in chronic cases with hepatic torpor, 333.  
*nitrous acid*, preferred in Hope's camphor mixture to nitric acid, 332.  
*opium*, lessens both peristalsis and secretions, to be used in serous, not in mucous diarrhœas, 65.  
*phenol*, as an intestinal antiseptic, 669.  
*rhubarb*, cathartic and astringent; of service in summer complaint, 504.  
*sodium phosphate*, useful in chronic diarrhœa of infants, 511.  
*strychnine*, in atonic cases, 139.  
*sulphuric acid*, an active astringent, 330.  
*syrup of lime*, 637.  
*tannalbin*, possesses the astringent properties of tannin without deleterious effects upon the stomach, 289.  
*tannic acid*, in serous types to check excessive secretion, 286.  
*tannoform*, claimed to combine antiseptic influence of formaldehyde to astringency of tannin, 290.  
*tannopine*, 289.  
*zinc oxide*, in chronic catarrhal varieties, 308.  
*zinc sulphate*, in chronic diarrhœa with ulcerations, 308.

**Digitalis-poisoning :**

- treatment of*, 233.

**Dilatation of Heart :**

- convallaria*, 247.  
*digitalis*, 227.

**Diphtheria :**

- antitoxin*, specific, use early and freely, 408.  
*benzoic acid*, locally as antiseptic, 692.  
*boric acid*, 698.  
*colloidal silver*, used by inunction, of doubtful value, 320.  
*creosote*, apply locally as antiseptic, 676.  
*hydrochloric acid*, to destroy membrane, 331.  
*hydrogen dioxide*, one of the most useful germicides, apply with swab, 662.  
*jaborandi*, 567.  
*lime-water*, to dissolve the membrane, 637.  
*mercury*, after antitoxin probably the most valuable internal remedy; calomel may be dusted on diseased surface, 367.  
*papain*, to dissolve membrane, 651.  
*phenol*, germicidal, may be used in form of lozenge, 669.  
*resorcinol*, antiseptic and feebly caustic, 685.  
*streptococcus antitoxin*, may be used for mixed infections, 411.  
*tincture of ferric chloride*, value doubtful, 328.

**Dislocation :**

- anæsthetics*, 22.

**Dropsy :**

- apocynum*, diuretic and cardiac stimulant, 237.  
*blisters*, in local dropsies, 603.  
*caffeine*, actively diuretic, 217.  
*calomel*, a powerful diuretic if used in large doses, 530.  
*cathartics*, 499.  
*convallaria*, is diuretic and sometimes cathartic, 247.  
*diaphoretics*, 561.  
*digitalis*, increases urinary secretion by stimulating the circulation, 229.  
*diuretics*, 527.  
*elaterin*, hydragogue cathartic, especially useful in renal dropsies, 519.

**Dropsy (Continued):**

- jaborandi*, eliminates the fluid through the skin, 567.
- jalap*, hydragogue cathartic, use in the form of compound jalap powder, 516.
- magnesium sulphate*, eliminates fluid through the bowels, 507.
- potassium nitrate*, 539.
- potassium bitartrate*, non-irritant diuretic, 539.
- scoparius*, diuretic but irritant to kidneys, 530.
- squill*, powerful diuretic, avoid in acute Bright's disease, 529.
- strophanthus*, cardiac stimulant, has more action on kidneys than *digitalis*, 241.
- sugar*, 544.
- theobromine*, useful in either cardiac or nephritic dropsy, 532.
- theocin*, diuretic 532.

**Dysentery :**

- calomel*, internally in fractional doses every hour, antiphlogistic and purgative, 515.
- castor oil*, purgative, also soothing to inflamed mucous membrane, 522.
- cathartics*, 499.
- cocaine*, in the form of suppositories when irritability of rectum, 126.
- copaiba*, in chronic cases, 553.
- creosote*, 676.
- enemata*, a very important part of the treatment of dysentery is the application of various drugs to the inflamed area by means of the high enema, 501.
- ergot*, useful in chronic cases, 588.
- flaxseed*, to be used freely in form of decoction, 619.
- glycerin*, applied locally by means of enema, 626.
- iodine*, 378.
- iodoform*, in the form of suppositories as local anodyne, 384.
- ipecacuanha*, except the purgatives *ipecac* in large doses the most valuable drug which can be given by mouth, 491.
- naphthol*, 681.
- nitrous acid*, in chronic dysentery of hot climates, 332.
- opium*, acts as antiphlogistic and analgesic, 65.
- potassium chlorate*, useful for rectal injections in chronic cases, 541.
- potassium permanganate*, wash out colon with one to two thousand solution, 660.
- silver nitrate*, by rectal injection in chronic cases, 317.
- sulphur*, seems to act as intestinal antiseptic, highly recommended, 694.

**Dysmenorrhœa :**

- amyl nitrite*, in spasmodic type, 168.
- antipyrine*, to relieve pain, 463.
- atropine*, in spasmodic type, 104.
- camphor*, in nervous cases, 191.
- cotton-root*, has stimulant action of the uterus, 598.
- hydrastinine hydrochlorate*, stimulant to uterus, 597.
- viburnum*, 581.

**Dyspepsia :**

- alcohol*, often relieves, but danger of habit, 205.
- antacids*, curative as well as alleviating, 631.
- asafetida*, in atonic cases, 17.
- calcium chloride*, recommended in fermentative cases, 637.
- charcoal*, as an absorbent in fermentative dyspepsia, 652.
- enemata*, 500.
- euonymus*, as a laxative, 520.
- ginger*, must not be used when there is inflammation, 482.
- hydrastis*, 595.
- hydrochloric acid*, as a digestant where insufficient gastric secretion, 331.
- magnesia*, laxative and antacid, 635.
- naphthol*, antiseptic, useful where much fermentation, 681.
- nitric acid*, to replace the hydrochloric acid of stomach, 332.
- pancreatin*, cannot have any effect as digestant, 649.
- pepper*, may be used in atonic types, 483.
- pepsin*, used where gastric secretion fails, usually of little benefit, 648.
- physostigma*, in intestinal dyspepsia, 151.



**Dyspepsia (Continued):**

- silver nitrate*, valuable astringent in true gastritis, especially when ulcer present, 317.
- soda*, corrects hyperacidity, encourages gastric secretion, 634.
- strychnine*, when associated with atony, 139.
- taraxacum*, 397.
- terebene*, in flatulent intestinal dyspepsia, 575.

**Dyspnœa :**

- aspidosperma*, active respiratory stimulant, 180.
- oxycamphor*, respiratory sedative and cardiac stimulant, 192.
- physostigma*, when dependent on bronchitis, 151.

**Eclampsia :**

See PUERPERAL CONVULSIONS.

**Eczema :**

- arsenic*, internally, beneficial in chronic cases, 351.
- betanaphthol*, oily solution, locally applied, 681.
- cacodylic acid*, an arsenical preparation, 359.
- glycerin*, useful emollient, 626.
- ichthargan*, 320.
- ichthyol*, a very useful external application, 396.
- menthol*, to relieve itching, 682.
- papain*, to destroy thickened skin, 651.
- resorcinol*, a valuable local application in chronic cases, 685.
- soft soap*, 600.
- suprarenal capsule*, to blanch reddened areas in chronic cases, 245.
- tannoform*, 290.
- zinc oxide ointment*, a useful astringent application, 309.

**Effusion, Pericardial :**

- potassium iodide*, aids the absorption of fluids, 377
- squill*, eliminates fluid through kidneys, 529.

**Effusion, Pleural :**

- antipyrine*, 464.
- iodoform*, as a substitute for iodides, 382.
- potassium iodide*, 377.
- squill*, 529.
- sugar*, diuretic, 544.

**Emesis :**

See VOMITING.

**Emphysema :**

- aspidosperma*, 180.

**Empyema :**

- creosote*, locally as disinfectant, 676.
- iodine*, inject after cleaning out cavity, 378.
- iodoform*, in tuberculous cases; glycerin solution locally applied, 384.

**Endocarditis :**

- aconite*, when cardiac excitement or excessive hypertrophy, 273.
  - camphor*, as a stimulant where immediate danger of heart failure, 191.
  - convallaria*, much disagreement as to its value, 247.
  - digitalis*, the most reliable stimulant and heart tonic in all cases where compensation is lost, 228.
  - mercury*, 367.
  - sparteine*, occasionally of service as heart stimulant, 250.
  - suprarenal extract*, value very doubtful, 246.
- See also HEART DISEASE.

**Endometritis :**

*hydrastinine hydrochlorate*, 597.  
*thyroid extract*, 496.

**Enteric Fever :**

See TYPHOID FEVER.

**Enteritis :**

*ammonium chloride*, 186.  
*bismuth*, the insoluble salts of bismuth (subnitrate, subcarbonate, subgallate, subsalicylate) are our most efficient remedies in enteritis, 306.  
*castor oil*, useful to cleanse the bowel, also sedative to inflamed mucosa, 521.  
*cathartics*, benefit by getting rid of irritating substance, use in beginning of treatment, 499.  
*chlorine*, recommended as an intestinal antiseptic, 659.  
*copper sulphate*, 310.  
*demulcents*, soothe the inflammation, use in acute cases, 617.  
*enemata*, 501.  
*flaxseed*, used as demulcent in the form of a decoction, 619.  
*hydrastis*, beneficial especially in chronic cases, 595.  
*magnesium sulphate*, a non-irritating cathartic, 507.  
*naphthalin*, as an intestinal disinfectant, 680.  
*opium*, should be used for antiphlogistic effects, not to check the diarrhœa, 65.  
*phenyl salicylate*, as intestinal antiseptic, 673.  
*physostigma*, in chronic cases, 151.  
*resorcinol*, 684.  
*silver nitrate*, 317.  
*slippery elm*, demulcent, 618.  
*tannalbin*, a non-irritant astringent, 289.  
 See also DIARRHŒA.

**Enuresis :**

See INCONTINENCE OF URINE:

**Ephemeral Fever :**

*aconite*, 273.

**Epididymitis :**

*silver nitrate*, painted over the scrotum, 317.

**Epilepsy :**

*acetanilid*, 469.  
*amyl nitrite*, in cases with a distinct aura, or in status epilepticus, 167.  
*anæsthetics*, rarely needed except in status epilepticus, 22.  
*antipyrine*, efficacious in some cases, may be tried in any, 463.  
*borax*, probably of no value, 698.  
*bromipin*, administered either hypodermically or by inunction, 160.  
*camphor*, 191.  
*chloretone*, recommended especially in petit mal, 92.  
*ergot*, increases effect of bromides, 589.  
*hydrastinine hydrochlorate*, theoretically is strongly indicated, 598.  
*hydrobromic acid salts*, the standard remedies, 157.  
*physostigma*, of very doubtful value, 151.  
*pituitary body*, no good, 407.  
*santonin*, 640.  
*silver nitrate*, useless, 317.  
*sulphonal*, 87.  
*zinc bromide*, by some believed of service, but doubtful if of value, 309.  
*zinc oxide*, 309.

**Episcleritis :**

*physostigmine*, 152.

**Epistaxis :**

*cocaine*, acts by constricting blood-vessels, 126.  
*gelatin*, may be employed with advantage both locally and internally, 401.  
*suprarenal extract*, a very powerful local constrictor of blood-vessels, 245.  
*tannic acid*, acts by coagulating blood and contracting vessels, 286.

**Epithelioma :**

*resorcinol*, as a caustic, 685.

**Erysipelas :**

*antipyrine*, to reduce the temperature, 462.

*atropine*, as a circulatory stimulant, 105.

*benzoic acid*, as an antiseptic, 692.

*boric acid*, saturated solution applied locally, 698

*creosote*, used in the form of an ointment, 676.

*ichthyol*, 396.

*iodine*, beneficial results from local application but must not be used too freely, 377.

*phenol*, deep injections, 669.

*streptococcus antitoxin*, has not fulfilled expectations, but may be tried, 410.

*tincture of ferric chloride*, specific action from internal use, 328.

**Excoriations :**

*glycerin*, soothing and softening, 626.

**Exophthalmic Goitre :**

*picric acid*, 647.

*sparteine*, to relieve the cardiac symptoms, 250.

*splenic extract*, well worth trying, 407.

*strophanthus*, to control the heart action, 241.

**Fatty Heart :**

See HEART DISEASE.

**Faucitis :**

See SORE THROAT.

**Favus :**

*naphthol*, in the form of a soap, 681.

**Fecal Accumulation :**

*black draught*, a very efficient remedy, 507.

*Epsom salt*, 507.

*senna*, 507.

**Feet, Sweating of :**

See HYPERIDROSIS.

**Feet, Tender :**

*tannic acid*, 286

**Felon :**

*carbolic acid*, injected deeply, 669.

*silver nitrate*, to abort, paint finger with solution of, 319.

**Fever :**

*acetanilid*, probably less depressant than antipyrin, 469.

*acetopyrin*, coal tar antipyretic, 466.

*aconite*, useful febrifuge in mild fevers, 273.

*alcohol*, acts as necessary food and cardiac stimulant, 203.

*ammonia*, to combat collapse, 185.

*antipyretics*, less serviceable than cold bath in severe fever, 445.

*antipyrine*, to lessen fever, 462.

*aspirin*, especially in rheumatic fever, 456.

*cardiac depressants*, increase heat elimination, 256.

*chloral*, as a sedative, 79.

*diaphoretics*, useful to break up some kinds of fever, 561.

*digitalis*, to maintain circulation, 231.

*diuretics*, water especially useful in febrile conditions, 527.

*gelsemium*, as arterial sedative in sthenic fevers, 173.

*hydrogen dioxide*, probably no value, 662.



**Fever (Continued):**

- jaborandi*, efficacious sudorific, 567.
  - lemon-juice*, as refrigerant drink, 513.
  - nitric acid*, 332.
  - oil of turpentine*, 551.
  - opium*, to support the system, 65.
  - phenacetin*, probably safest of coal-tar antipyretics, 471.
  - phenocoll hydrochloride*, 472.
  - salicylic acid*, not generally useful as antipyretic, 451.
  - saloquinine*, 437.
- See also TYPHOID FEVER, SCARLET FEVER, etc.

**Fibroid Tumors of Uterus:**

See UTERUS, FIBROID TUMORS OF.

**Fissure of Anus:**

- atropine*, to relieve accompanying spasm, 104.
- benzoic acid*, antiseptic and healing, 693.
- cocaine*, as a local anæsthetic, 126.
- iodoform*, a valuable local anæsthetic, 382.

**Fistula:**

*creosote*, 676.

**Flatulence:**

- aromatics*, to stimulate intestinal peristalsis, 479.
  - asa fetida*, enemata in flatulent constipation, 17.
  - Hoffmann's anodyne*, carminative, 29.
  - physostigma*, a stimulant to intestinal muscle, 151.
- See also COLIC.

**Fractures:**

- calcium phosphate*, in ununited fractures, 336.
- sulphonol*, to relieve muscular spasm, 84.
- thyroid extract*, has sometimes proved useful in delayed union, 406.

**Frost-Bites:**

*ichthyol*, 396.

**Furuncles:**

See BOILS.

**Galactorrhœa:**

- antipyrine*, 464.
- belladonna*, either internally or applied locally to breasts, 105.
- ergot*, 588.

**Gall-Stones:**

See CALCULI.

**Gangrene:**

*nitric acid*, 332.

**Gangrene of the Lungs:**

*phenol*, 669.

**Gastralgia:**

- arsenic*, in neuralgic types, 352.
- bismuth*, especially in feeble patients, 306.
- hydrocyanic acid*, a useful remedy, probably acts on sensory nerves, 280.
- manganese dioxide*, 329.
- orthoform*, useful in cases of gastric ulcer, 52.
- phenol*, of value on account of local anæsthetic action as well as antiseptic, 668.

**Gastric Crisis:**

See LOCOMOTOR ATAXIA.

**Gastric Ulcer :**

*copaiba*, as a stimulant in chronic and indolent ulcers, 553.  
*ichthargan*, a combination of silver and ichthyol, 321.  
*orthoform*, to lessen pain through local anæsthetic effect, 52.  
*resorcinol*, a not generally useful remedy, 684.  
*silver nitrate*, the standard remedy, sedative, astringent, and antiseptic, 317

**Gastric Uneasiness :**

*antacids*, 631.

**Gastritis :**

*ammonium chloride*, in chronic cases, 186.  
*bismuth*, all its insoluble salts act similarly; they are sedative, astringent protective, and antiseptic, 306.  
*calcium chloride*, 637.  
*demulcents*, in acute inflammations may be freely employed, 617.  
*hydrastis*, useful especially in chronic cases, 595.  
*ichthargan*, 321.  
*silver nitrate*, useful sedative astringent, 317.  
 See also DYSPEPSIA.

**Gelsemium Poisoning :**

*treatment of*, 174.

**Glands, Enlarged :**

*cod-liver oil*, to improve nutrition in scrofula, 390.  
*ichthyol*, applied externally, 396.  
*iodine*, used externally in indolent hypertrophy, 378.  
*iodoform*, either by mouth (382) or glycerin solution injected into tuberculous glands, 384.  
*phenol*, deeply injected, 669.  
*sulphurated lime*, 694.  
*thiosinamine*, especially in cases with fibrous tissue, 398.

**Glaucoma :**

*dionine*, used locally increases the flow of lymph in the eye, 74.  
*physostigmine*, relieves ocular tension by contracting the pupil, 152.  
*salicylic acid*, useful especially in rheumatic cases, 452.

**Gleet :**

*cantharides*, a powerful stimulant to the urethral mucous membrane, 606.  
*tincture of ferric chloride*, in combination with cantharides, 328.  
*turpentine*, a stimulant alterative diuretic, 551.

**Glycosuria :**

See DIABETES MELLITUS.

**Goitre :**

*fluorides*, 659.  
*iodine*, useful in true goitre, 376.  
*thyroid extract*, only in simple goitre, not in exophthalmic, 406.

**Goitre, Exophthalmic :**

See EXOPHTHALMIC GOITRE.

**Gonorrhœa :**

*acetozone*, locally as antiseptic, 663.  
*albagin*, a silver preparation, 319.  
*antimony*, internally as a circulatory depressant and diaphoretic, 260.  
*argoin*, a silver preparation, 320.  
*benzoic acid*, internally as urinary antiseptic, 693  
*betol*, given internally, 681.  
*bismuth*, used locally in early stages, 306.  
*copaiba*, in the beginning stages employed internally, 553.  
*hydrastis*, locally in the later stages, 595.  
*hydrogen dioxide*, 662.

**Gonorrhœa (Continued):**

- ichthargan*, active silver preparation, 320.
- kava*, 556.
- largin*, recommended especially in gonorrhœa in women, 319.
- matico*, 554.
- methylen-blue*, of doubtful value, 439.
- oil of erigeron*, 555.
- oil of sandal-wood*, used internally in the advanced stages, 555.
- pareira*, in chronic gonorrhœa as alterative diuretic, 547.
- potassium bromide*, to allay sexual excitement, 158.
- protargol*, an organic silver preparation, 321.
- quinine*, applied locally, 432.
- resorcinol*, 684.
- silver citrate*, claimed to be non-irritant and actively germicidal, 319.
- silver nitrate*, especially useful in chronic cases, 316.
- silver sulphocarbolate*, 319.
- terpin hydrate*, used internally, 575.
- zinc acetate*, 309.

**Gout:**

- cathartics*, 500.
- colchicum*, most useful in typical gout (podagra), 393.
- ichthyol*, as an external application, 396.
- lithium*, supposed to be depurant and to increase solubility of urates, 543.
- magnesia*, antacid and laxative, 635.
- piperazine*, occasionally useful in chronic cases, 543.
- potassium iodide*, of some service in irregular or chronic gout, 376.
- salicylates*, used in combination with colchicum, 451.
- sulphur*, 694.
- sulphuretted hydrogen*, in chronic cases, 578.
- water*, 526.

**Granular Conjunctivitis:**

See CONJUNCTIVITIS.

**Granulations, Exuberant:**

- burnt alum*, caustic and astringent, 616.
- copper sulphate*, antiseptic astringent and mildly caustic, 616.
- silver nitrate*, caustic and powerfully germicidal, 316.
- zinc sulphate*, 616.

**Gravel:**

- benzoic acid*, probably lessens uric acid excretion, 863.
- potassium salts*, renders urine alkaline, also lessens formation of uric acid, 538.
- soda*, less valuable than potash salts, 634.

**Graves's Disease:**

See EXOPHTHALMIC GOITRE.

**Grippe:**

See INFLUENZA.

**Gummata:**

See SYPHILIS.

**Gums, Retraction of:**

*iodine*, applied locally by means of camel's-hair brush, 378.

**Hay Fever:**

- antitoxin*, 411.
- atropine*, to check excessive nasal secretion, 105.
- cocaine*, applied locally, relieves congestion and is anæsthetic, 126.
- quinine*, locally applied, probably not of much value, 432.
- resorcinol*, 684.
- suprarenal extract*, probably the most useful remedy known for local application, 245.



**Headache :**

*ammonia*, when due to sick stomach, 632.  
*ammonium valerate*, 16.  
*antacids*, in gastric headaches to correct hyperacidity, 632.  
*antipyrine*, promptly acting coal-tar analgesic, 463.  
*caffeine*, especially useful in conjunction with coal tars, 216.  
*camphor*, in nervous types, 191.  
*emetics*, 487.  
*ergot*, in congestive headaches, 589.  
*ether*, in hysterical or nervous cases, 30.  
*magnesia*, antacid laxative in cases with gastric disturbances, 635.  
*phenacetin*, one of the most valuable of the coal tars, 471.  
*strychnine*, when associated with optic atrophy, 138.  
 See also MIGRAINE and NEURALGIA.

**Heartburn :**

See CARDIALGIA.

**Heart Disease :**

*adonidin*, a heart stimulant, 252.  
*apocynum*, acts on the heart like digitalis but is more diuretic, 237.  
*caffeine*, useful as a temporary stimulant, 217.  
*convallaria*, employed especially when dropsy, 247.  
*digitalis*, the most useful drug known in all forms of prolonged heart failure  
 is both stimulant and tonic to heart muscle, 227.  
*mercury*, as an antiphlogistic in acute endocarditis, 367.  
*sparteine*, 250.  
*strophanthus*, very similar to digitalis, but more prompt and less powerful, 241.  
*strychnine*, especially valuable where muscular weakness or degeneration, 139.  
*suprarenal extract*, of doubtful utility, 246.  
 See also ENDOCARDITIS, ANGINA PECTORIS.

**Heart Failure :**

*alcohol*, promptly acting, not very powerful, 204.  
*ammonia*, must be given hypodermically to have an effect, 185.  
*amyl nitrite*, 168.  
*caffeine*, useful in cases not too acute, 217.  
*camphor*, hypodermically in olive oil, a very powerful resuscitant, 191.  
*digitalis*, 230.  
*strophanthus*, 241.  
*suprarenal extract*, a dangerous drug, 245.

**Heart, Palpitation of :**

*convallaria*, 247.  
*sparteine*, 250.

**Hematemesis :**

*gelatin*, increases the coagulability of blood, especially useful in subacute cases, 401.  
*Monse's solution*, one of the most trustworthy styptics in acute cases, 327.  
*suprarenal extract* acts by constricting vessels at bleeding point, 245.  
*tannic acid*, 286.  
*vinegar*, useful especially in emergencies—is quite efficient, 290.

**Hematuria :**

*gallic acid*, perhaps the most generally useful remedy, 287.  
*gelatin*, believed by some to be irritant to kidneys, is probably beneficial, 401.  
*turpentine*, in passive hemorrhage, 551.  
 See also BLACK-WATER FEVER.

**Hemophilia :**

*gelatin*, 401.

**Hemoptysis :**

*alum*, used by atomization, 292.  
*atomization*, as a means of applying remedies locally to lungs, 572.  
*cotarnine*, 291.

**Hemoptysis (Continued):**

- ergot*, commonly used, but doubtful if of service, 588.
- gallic acid*, given internally, 287.
- gelatin*, probably most useful drug known (except opiates); increases coagulability of blood, 401.
- ipecacuanha*, claimed to be specific, 492.
- lead acetate*, doubtful if of service, 294.
- Monse's solution*, applied by atomization, 327.
- oil of turpentine*, 551.
- opium*, some form of opium or morphine should always be given, 64.

**Hemicrania:**

See MIGRAINE.

**Hemiplegia:**

*strychnine*, avoid during early stages, later useful as general tonic, 138.

**Hemorrhage from the Bowels:**

- oil of turpentine*, 551.
- suprarenal extract*, acts locally by constricting vessels, 245.
- tannic acid*, best given in form of crude galenical rather than pure tannin, 286.

**Hemorrhages:**

- alum*, precipitates albumin of blood, forming hard coagulum, 292
- astringents*, 284.
- cocaine*, applied locally powerfully constricts vessels, 126.
- cotarnine*, highly praised in both internal and local bleeding, 291.
- creosote*, useful only to check capillary oozing, 675.
- ergot*, widely used but probably no good, 588.
- gelatin*, hastens the clotting of blood, useful either locally or internally, 401.
- ipecacuanha*, 492.
- lead acetate*, 294.
- matico*, in external hemorrhages, acts mechanically, 554.
- Monse's solution*, a powerful styptic and astringent when locally applied, 327.
- oil of erigeron*, 555.
- oil of turpentine*, 551.
- sulphuric acid*, 331.
- suprarenal extract*, locally applied, a very useful drug, contracts blood-vessels, 245.
- tannic acid*, for local application, 288.

**Hemorrhoids:**

- aloes*, as a laxative, 506.
- belladonna*, as a local anodyne, 106.
- cocaine*, local anæsthetic and constrictor of blood-vessels, 126.
- cubebs*, used internally in chronic types, 554.
- enemata*, 500.
- glycerin*, used as laxative, 626.
- infiltration anæsthesia*, for operative purposes, 54.
- iodoform*, in suppositories a very useful anodyne, 382.
- potassium chlorate*, saturated solution injected into the rectum a useful treatment, 541.
- sulphur*, as a laxative, 694.
- tannic acid*, useful astringent in form of ointment, 286.
- tobacco*, 175.

**Hepatic Congestion and Torpor:**

- ammonium chloride*, a useful remedy in chronic cases, 186.
- calomel*, probably most generally serviceable remedy in acute cases, 515.
- cathartics*, 499.
- chlorine*, 659.
- emetics*, 487.
- euonymus*, used in chronic cases, 520.
- ipecacuanha*, frequently of service, 491.
- lemon-juice*, employed in habitual hepatic torpor, 513.
- nitric acid*, 332.

**Hepatic Congestion and Torpor** (*Continued*):

- nitro-hydrochloric acid*, one of the best remedies in chronic cases, 333.
- potassium salts*, act as depurants by increasing oxidation, 538.
- soda*, in chronic cases, 634.
- sodium phosphate*, of value in chronic cases with constipation, 511.

**Hepatitis :**

- ammonium chloride*, in chronic cases, 186.
- mercury*, as antiphlogistic rather than purgative, 367.
- nitro-hydrochloric acid*, in chronic cases, may be used internally or in form of bath, 333.

**Herpes :**

- naphthol*, in the form of a soap, 681.
- salicylic acid*, useful in corneal herpes, 452.

**Hiccough :**

- atropine*, 104.
- chloral*, acts by depression of motor centres, 80.
- ether*, acts locally on stomach, also on nervous centres, 30.
- musk*, claimed to be almost a specific, 15.
- sulphonal*, antispasmodic effect, 84.

**Hospital Gangrene :**

- bromine*, a very active caustic and germicidal agent, 616.
- nitric acid*, actively caustic, 332.

**Hydrocele :**

- iodine*, inject directly into sac, 378.
- phenol*, deep injections of, 669.

**Hydrocephalus :**

- potassium iodide*, 377.

**Hydrophobia :**

- caustic potash*, applied to bite as a prophylactic, 612.
- escharotics*, 611.

**Hyperacidity :**

- See ACIDITY OF STOMACH.

**Hyperemesis :**

- See VOMITING.

**Hyperidrosis :**

- arsenic*, internally in neurotic cases, 351.
- chalk*, applied locally as a desiccant, 637.
- tannic acid*, used in form of wash, 286.
- tannoform*, astringent and antiseptic dusting powder, 290.
- See also NIGHT-SWEATS.

**Hyperpyrexia :**

- See FEVER.

**Hypertrophy of Heart :**

- aconite*, 273.

**Hypochondriasis :**

- alcohol*, 205.
- cypripedium*, 19.

**Hysteria :**

- anæsthetics*, to check convulsions, 21.
- antipyrine*, in convulsive cases, 462.
- asafetida*, a useful nerve sedative, 17.



**Hysteria (Continued):**

*bromides*, probably the most widely used remedies, 157.  
*camphor*, useful as a nerve sedative and anticonvulsant, 191.  
*cocaine*, as a stimulant and stomachic, 126.  
*conium*, 178.  
*creosote*, to check hysterical vomiting, 675.  
*ether*, given internally, 30.  
*gold and sodium chloride*, 373.  
*monobromated camphor*, 161.  
*musk*, 15.  
*oil of wormseed*, 643.  
*sparteine*, 250.  
*sumbul*, especially in cases with uterine disturbances, 17.  
*valerian*, a mildly acting but widely useful drug, 16.

**Ichthyosis :**

*naphthol*, 681

**Idiocy :**

*thyroid extract*, valuable probably only in myxœdematous subjects, 406.

**Ileus :**

See **INTESTINAL OBSTRUCTION.**

**Impotence :**

*turpentine*, 551.  
*yohimbine*, useful only in neurasthenic cases, not in organic, 556

**Incontinence of Urine :**

*antipyrine*, in spasmodic cases, 463.  
*atropine*, when due to irritability of bladder, 104.  
*chloral*, in spasmodic cases, 80.  
*quinine*, in large doses frequently useful, 430.  
*strychnine*, when due to nervous relaxation, 139.  
*turpentine*, in atonic forms, 551.

**Indigestion :**

See **DYSPEPSIA.**

**Infantile Colic :**

See **COLIC.**

**Infantile Convulsions :**

See **CONVULSIONS.**

**Infantile Diarrhœa :**

See **CHOLERA INFANTUM.**

**Inflammations :**

*belladonna*, locally applied as anodyne, 105.  
*blisters*, useful in serous and other internal inflammations, 603.  
*carbolic acid*, deep injections, in deep-seated inflammations of chronic type, 669.  
*lead acetate*, sedative astringent embrocation, especially in acute conditions, 294.  
*mercury*, especially valuable in serous inflammations, may be used internally or externally, 367.  
*opium*, seems to exercise a specific antiphlogistic effect, 65.  
*silver nitrate*, applied locally to inflamed mucous membranes, 317.  
*solution of lead subacetate*, 294.  
*tartar emetic*, to quiet arterial excitement in sthenic inflammations, 260

**Influenza :**

*aconite*, to encourage sweating, 273.  
*betanaphthol*, 681.  
*pilocarpine*, used to produce sweat will sometimes abort, 567.

**Insanity :**

- chloretone*, used as a somnifacient, uncertain, 92.
- hyoscine hydrobromide*, acts as hypnotic and in some cases seems to have curative effect, 110.
- paraldehyde*, one of the most valuable somnifacients, 88.
- spleen extract*, 407.
- vernal*, as a hypnotic, 91.
- See also MANIA.

**Insomnia :**

- See SLEEPLESSNESS.

**Intermittent Fever :**

- See MALARIA.

**Intertrigo :**

- chalk*, protective and desiccant, 637.
- ichthyol*, 396.

**Intestinal Atony :**

- physostigma*, the most useful stimulant to unstriated muscle fibre known, 151.

**Intestinal Catarrh :**

- See ENTERITIS.

**Intestinal Indigestion :**

- betanaphthol*, to check fermentation, 681.
- physostigma*, 151.
- salol*, antiseptic, 673.

**Intestinal Obstruction :**

- atropine*, when due to intestinal spasm, 104.
- opium*, in spasmodic or irritative types, 65.

**Iritis and Irido-cyclitis :**

- atropine*, to rest eye and prevent adhesions, best mydriatic for this purpose, 106.
- dionine*, increases the flow of lymph in eye, 74.
- mercury*, in cases with marked lymphatic exudation, 367.
- salicylic acid*, especially but not exclusively useful in rheumatic persons, 452.
- santonin*, in amaurosis following iritis, 640.
- thiosinamine*, probably of very little value, 398.

**Irritable Bladder :**

- See BLADDER, IRRITABLE.

**Irritable Heart :**

- digitalis*, 229.

**Itch :**

- See SCABIES.

**Ivy-Poisoning :**

- See RHUS-TOXICODENDRON POISONING.

**Jaundice :**

- ammonium chloride*, in chronic torpor of the liver and catarrhal jaundice, 186.
- emetics*, to relieve portal congestion, 487.
- forced enemata*, 501.
- ipecacuanha*, 491.
- lemon-juice*, in catarrhal jaundice, 513.
- mercury*, probably the most generally serviceable drug in catarrhal jaundice and acute biliousness, 515.
- nitro-hydrochloric acid*, especially valuable in cases depending on chronic hepatic torpor, 333.
- oxgall*, most powerful stimulant to hepatic secretion known, 508.

**Jaundice (Continued):**

- potassium salts*, depurant and alkaline; useful in chronic hepatic torpor and catarrhal jaundice, 538.
- sodium phosphate*, in chronic cases with constipation, 511.
- sodium salts*, alkalies of value, 634.

**Joints, Inflammation of:**

- blisters*, in chronic cases, 603.
- cautery*, 604.
- cod-liver oil*, in tuberculous joint diseases, 390.
- gold and sodium chloride*, 377.
- ichthyol*, especially in gouty or rheumatic forms,
- iodine*, internally as alterative (376) or externally as a counter-irritant, 378.
- iodoform*, injected into the joint directly, in tuberculous arthritis, 384.

**Keloid:**

- ichthyol*, locally applied, 396.
- thiosinamine*, may be used either internally or injected locally, 398.
- thyroid extract*, recommended highly for internal use, 403.

**Keratitis:**

- atropine*, to lessen liability to iritis, 106.
- dionine*, increases lymph flow in eye, 74.
- iodipin*, 380.
- physostigmine*, to reduce vascularization, 152.
- salicylic acid*, especially, but not exclusively, useful in rheumatic cases, 452.

**Labor:**

- anæsthetics*, to allay the suffering, 22.
- chloral*, to lessen pain and overcome rigidity of os, 80.
- ergot*, to increase uterine contractions, used only in later stages, 586.

**Laryngismus stridulus:**

- antipyrine*, 463.
- atropine*, 104.
- chloral*, 80.
- expectorants*, 571.

**Laryngitis:**

- camphor-menthol*, dissolved in liquid petrolatum and used as spray, (note) 682.
- cocaine*, applied locally as palliative, 126.
- gelsemium*, internally in spasmodic types, 173.
- glycerin*, locally applied has a demulcent effect, 626.
- heroin*, used as local anæsthetic in laryngeal tuberculosis, 75.
- ichthargan*, a solution in glycerin as a spray, 320.
- lactic acid*, as a caustic in tuberculous laryngitis, 616.
- mercury*, administered internally as antiphlogistic, 367.
- menthol*, dissolved in liquid petrolatum and applied by atomization, 682.
- naphthol*, 681.
- orthoform*, a valuable local anæsthetic in tuberculous laryngitis, 52.
- pilocarpine*, 567.
- silver nitrate*, two per cent. solution applied locally, 316.
- steam atomizer*, a very useful method of applying drugs locally, 572.
- suprarenal capsule*, 245.

**Lead Poisoning:**

- alum*, recommended in colica pictonum, 292.
- atropine*, most valuable remedy for lead colic known, 104.
- potassium iodide*, to increase elimination of lead in chronic poisoning, 377.
- strychnine*, of value in plumbic poliomyelitis, 138.
- sulphuric acid*, chemical antidote, 331.
- treatment of acute*, 295.
- treatment of chronic*, 301.



**Lepra :**

*ichthyol*, 396.  
*thiosinamine*, 398.

**Leucorrhœa :**

*bismuth subnitrate*, sedative astringent, 306.  
*creosote*, disinfectant, 676.  
*iodine, tincture of*, locally applied, 378.  
*potassium permanganate*, disinfectant and deodorant, 660.  
*resorcinol*, 684.  
*tannic acid*, astringent, 286.

**Leukæmia :**

*cacodylic acid*, of no more value than official forms of arsenic, 359.  
*ergot*, injected hypodermically, 589.

**Lichen :**

*arsenic*, 351.

**Lipoma :**

*ichthyol*, 396.

**Lithæmia :**

See URIC ACID DIATHESIS.

**Liver Diseases :**

See HEPATIC.

**Lobelia Poisoning :**

*treatment of*, 172.

**Locomotor Ataxia :**

*acetanilid*, for relief of pain, 469.  
*antipyrine*, for painful crises, 463.  
*aspirin*, as analgesic, 456.  
*glycero-phosphates*, as nerve tonic, 337.  
*hyoscine*, as analgesic, 111.  
*silver nitrate*, used to affect conditions in cord, but of doubtful service, 317.

**Lumbago :**

*ichthyol*, applied locally, 396.  
*potassium iodide*, in subacute types, 376.  
*salicylates*, the standard remedy, 451.  
*sulphur*, 694.

**Lumbrici :**

See ROUND-WORMS

**Lupus :**

*aristol*, as a dusting powder, 387.  
*arsenic*, as a caustic, 613.  
*cantharidin*, (note) 605.  
*guaiacol*, actively germicidal, 676.  
*ichthyol*, 396.  
*phosphorus*, internally as a tonic alterative, 340.  
*pyrogallol*, an ointment used as a caustic, 616.  
*thiosinamine*, 398.  
*thyroid extract*, 406.

**Lymphadenitis :**

*ichthyol*, applied externally in form of ointment, 396.  
*sulphurated lime*, used internally, 694.  
See also SCROFULOSIS.

**Lymphoma :**

*arsenic*, 351.

**Malaria :**

- ammonia*, as a heart stimulant in malarial collapse, 185.  
*amyl nitrite*, will abruptly end a chill; perhaps useful in pernicious type, 168.  
*aristochin*, an almost tasteless ester of quinine, 436.  
*arsenic*, useful especially in chronic or irregular malarias; also in convalescence from acute ague, 350.  
*chloroform*, may be used to abort a chill, 34.  
*cinchonine*, similar to but less powerful than quinine, 435.  
*counter-irritants*, in the collapse of pernicious malaria, 603.  
*diaphoretics*, to shorten duration of paroxysm, 561.  
*eucalyptus*, frequently of service when quinine contraindicated, 442.  
*euquinine*, a tasteless substitute for quinine, 436.  
*gelsemium*, 173.  
*methylene-blue*, a very powerful antiperiodic, especially valuable where hæmaturia, 438.  
*piperine*, 483.  
*quinine*, the standard remedy, best given immediately before paroxysm, 430.  
*saloquinine*, 437.  
*Warburg's tincture*, probably the most effectual combination known against the more severe types of the disease, 436.

**Malarial Neuralgia :**

- arsenic*, as an adjunct to cinchona alkaloids, 350.  
*quinine*, large doses required to produce an effect, 431.

**Malignant Pustule :**

- escharotics*, 611.

**Mania :**

- atropine*, when disease dependent on exhaustion, as puerperal mania, 105.  
*cathartics*, as revulsants, 500.  
*chloral*, for its somnifacient effect, 79.  
*conium*, to lessen the motor excitement, 178.  
*croton oil*, as a revulsant, 522.  
*hyoscine hydrobromate*, seems to have some curative effect as well as general sedative action, 110.

**Mania a Potu :**

- See DELIRIUM TREMENS.

**Mastitis :**

- belladonna plaster*, 106.

**Masturbation :**

- heroine*, claimed to be a sexual sedative, 75.  
*bromides*, the most generally serviceable sexual sedatives known, 158.

**Melancholia :**

- alcohol*, will often relieve symptoms, but great danger of habit, 205.  
*cocaine*, of very little service, 126.  
*thyroid extract*, may be tried, but not likely to be successful, 406.

**Membranous Croup :**

- See CROUP.

**Ménière's Disease :**

- pelletierine*, 646.

**Meningitis :**

- cautery*, the most active form of counter-irritation, 604.

**Menorrhagia :**

- aloes*, when constipation; acts as laxative and tends to pelvic hyperæmia, 506.  
*calcium phosphate*, when associated with anæmia, 336.  
*cotarnine*, 291.  
*creosote*, applied locally, 670.

**Menorrhagia (Continued):**

- digitalis*, claimed to act as a stimulant to uterine muscles, 231.
- ergot*, perhaps the most generally efficient remedy known, 588.
- gelatin*, increases coagulability of blood, may be used both internally and locally, 401.
- hydrastis*, 595.
- hydrastinine hydrochlorate*, probably acts by causing contraction of womb, 597.
- oil of erigeron*, 555.
- savine*, useful only in conditions of relaxation, 579.
- suprarenal extract*, given internally, probably causes uterine contraction, 246.
- thyroid extract*, 406.
- viburnum*, 581.

**Menstruation, Suppression of:**

See AMENORRHOEA.

**Mercurial Ptyalism:**

See PTYALISM.

**Metritis:**

- bismuth oxyiodogallate*, employed in form of suppositories, 307.
- creosote*, as a disinfectant, especially in puerperal cases, 676.
- ergot*, in chronic cases, 588.

**Metrorrhagia:**

- ergot*, acts by stimulating uterine muscle, 588.
- gelatin*, increases coagulation of blood, 401.
- hydrastinine hydrochlorate*, 597.

**Migraine:**

- acetopyrin*, coal-tar analgesic, 466.
- amyl nitrite*, in cases with spasm of capillary blood-vessels, 169.
- antipyrine*, during paroxysm, to relieve headache, 463.
- aspirin*, 456.
- caffeine*, sometimes promptly relieves headache, at others fails, 216
- cannabis indica*, used as curative between paroxysms 117
- cocaine*, 126.
- pyramidon*, 472.

**Mitral Disease:**

See HEART DISEASE.

**Morphine-Poisoning:**

See OPIUM-POISONING.

**Morphœa:**

*arsenic*, 351.

**Multiple Sclerosis:**

*acetanilid*, 469.

**Muscarine Poisoning:**

*atropine*, counteracts effects of poison on inhibitory and secretory nerves, 105.

**Muscular Rheumatism:**

See RHEUMATISM.

**Mush-Room Poisoning:**

See MUSCARINE POISONING.

**Myelitis:**

- phosphorus*, as a reconstructive tonic for nerve centres, 340.
- silver nitrate*, value questionable, 317.

**Myocarditis:**

See HEART DISEASE.



**Myopathy :**

*thyroid extract*, 406.

**Myxœdema :**

*thyroid extract*, is a specific, 405.

**Narcotic Poisoning :**

See POISONING.

**Nasal Catarrh :**

See RHINITIS.

**Nausea :**

See SICK STOMACH.

**Nephritis :**

See BRIGHT'S DISEASE.

**Nervous Exhaustion :**

See NEURASTHENIA.

**Nervous Vomiting :**

See VOMITING.

**Nervousness :**

*asafetida*, in cases of hysterical type, 17.

*camphor*, a very useful sedative, 190.

*arsenic*, especially but not exclusively useful in malarial cases, 157.

*valerian*, useful in milder forms of hysteria, 16.

**Neuralgia :**

*aconite*, applied locally, 273.

*alcohol*, grave danger of formation of habit, 205.

*antipyrine*, one of the best analgesics, 463.

*arsenic*, especially but not exclusively useful in malarial cases, 351.

*aspirin*, of service in nervous as well as rheumatic types, 456.

*blisters*, 604.

*caffeine*, very markedly increases the analgesic power of other antineuralgics, especially the coal-tar products, 216.

*cannabis indica*, used both as an anodyne and as a curative, 117.

*carbon disulphide*, employed locally as a counter-irritant, 610.

*chloroform*, in the form of a liniment, 34.

*cod-liver oil*, 390.

*ether*, internally sometimes of service, 30.

*gelsemium*, used especially as a curative agent in recurring neuralgias, 174.

*hydrocyanic acid*, in neuralgia of the stomach, 280.

*iodoform*, when syphilitic origin, 382.

*methylene-blue*, not so useful as other aniline derivatives, 438.

*phosphorus*, when due to nervous exhaustion, 340.

*potassium bromide*, very frequently of service, especially in combination with caffeine, 157.

*potassium iodide*, in rheumatic or syphilitic cases, 376.

*pyramidon*, 472.

*quinine*, especially in periodic types, even if not malarial, 431.

*salokinine*, 437.

*veratrine*, used externally in form of ointment, but is a dangerous remedy, 266.

See also HEADACHE.

**Neuralgia, Intermittent :**

See MALARIAL NEURALGIA.

**Neuralgia, Rheumatic :**

See RHEUMATIC NEURALGIA.

**Neurasthenia :**

- bromopin*, a preparation of bromine, 160.
- cocaine*, as a nerve stimulant and tonic, 126.
- digitalis*, when circulation is feeble, 230.
- quinine*, as general tonic, 436.
- glycero-phosphates*, supposed to represent phosphorus in easily assimilable form, but of unproved value, 337.
- gold and sodium chloride*, used as nerve alterative, value doubtful, 373.
- hops*, mildly sedative, useful in nervous unrest, 18.
- hypophosphites*, 336.
- paraldehyde*, as a hypnotic, 88.
- phosphorus*, increases reconstructive metabolism of nerve centres, frequently of great service, 339.
- sparteine*, to relieve cardiac palpitation, 250.
- strychnine*, especially useful in chronic cases, 138.
- Warburg's tincture*, in acute nervous exhaustion, 436.

**Neuritis :**

- acetopyrin*, to lessen pain, 466.
- aconite*, rarely of value, may be used locally, 273.
- atropine*, in cases with local muscular spasm, 104.
- blisters*, the most generally useful form of counter-irritation, repeat frequently as necessary, 603.
- cautery*, often valuable in chronic cases, 604.
- methylene-blue*, to relieve pain, 438.
- salicylates*, in rheumatic cases, 451.
- saloquinine*, combination of quinic and salicylic acids, 437.

**Night-Pains, Syphilitic :**

- iodoform*, 382.

**Night-Sweats :**

- agaric*, a very frequently useful remedy, 291.
- alum*, to be employed externally, 292.
- atropine*, the most generally serviceable remedy known, 105.
- camphoric acid*, 192.
- dionine*, especially useful in phthisis, as it is also cough sedative, 73.
- ergot*, in cases with passive relaxation of blood-vessels, 588.
- gallic acid*, 287.
- sulphonal*, 84.
- sulphuric acid*, one of the best remedies, 330.

**Nipples, Sore :**

- benzoic acid*, best applied in form of compound tincture of benzoin, antiseptic and protective, 693.
- tannic acid*, for purpose of hardening, 286.

**Nocturnal Emissions :**

- See SPERMATORRHEA.

**Nocturnal Enuresis :**

- See INCONTINENCE OF URINE.

**Nymphomania :**

- bromides*, in conjunction with hyoscine most efficacious remedy, 158.
- heroine*, recommended as sexual sedative, 75.
- hyoscine hydrobromate*, has especial action on sexual centres, 111.

**Obesity :**

- saccharin*, as a sweetening agent free from objections to sugar, 627.
- thyroid extract*, will reduce weight temporarily more certainly than any other drug, 405.

**Obstruction of Bowels :**

- See INTESTINAL OBSTRUCTION.

**Onychia Maligna :**

*corrosive sublimate*, powerfully germicidal, mildly caustic, 614.  
*lead nitrate*, to be powdered on inflamed area, 294.

**Ophthalmia :**

*iodine*, used in scrofulous cases, 378.  
*salicylic acid*, in sympathetic ophthalmia, 452.  
*silver acetate*, in ophthalmia neonatorum, 319.

**Opium-Habit :**

*cocaine*, 126.  
*treatment of*, 71.

**Opium-Poisoning :**

*atropine*, as respiratory stimulant, 105.  
*caffeine*, respiratory and cerebral excitant, 216.  
*potassium permanganate*, as chemical antidote, 660.  
*treatment of*, 68.

**Osmidrosis :**

*tannic acid*, 286.

**Osteomalacia :**

*calcium phosphate*, 335.  
*phosphorus*, 340.

**Osteoporosis :**

*phosphorus*, 340.

**Otitis :**

*betanaphthol*, as an antiseptic, 681.  
*resorcinol*, in chronic cases, 684.

**Otorrhœa :**

*creosote*, as a disinfectant in fetid types, 676.  
*hydrastis*, acts directly on mucous membrane, 595.  
*potassium permanganate*, oxidizing disinfectant, 660.

**Ovarian Irritation :**

*viburnum*, 581.

**Oxalic Acid Diathesis :**

*nitric acid*, 332.  
*nitro-hydrochloric acid*, a specific in neurasthenic oxaluria, 333.

**Oxalic-Acid Poisoning :**

*treatment of*, 686.

**Oxyuris Vermicularis :**

See SEAT-WORMS.

**Ozæna :**

*iodine*, an alterative stimulant, 378.  
*potassium permanganate*, disinfectant, 660.

**Pain :**

*acetanilid*, when pain of nervous origin, 469.  
*aconite*, locally applied in neuralgia and similar conditions, 273.  
*anæsthetics*, of service in severe medical as well as surgical conditions, 21.  
*antipyrine*, in various nervous pains whether functional or organic, 463.  
*atropine*, as local anodyne, 106.  
*cannabis indica*, frequently of service although not very powerful, 117.  
*chloral*, of little use as analgesic, 80.  
*chloroform*, externally as counter-irritant, 34.  
*iodoform*, as a local anæsthetic, 382.



**Pain (Continued):**

*methylene-blue*, similar to, generally less useful than other aniline derivatives, 438.  
*opium*, the most generally efficient drug, but danger of habit, 64.  
*phenacetin*, useful in nervous pains, especially in combination with caffeine, 471.

**Palpitation of Heart:**

See HEART, PALPITATION OF.

**Papilloma:**

*resorcinol*, 685.

**Paralysis:**

*strychnine*, useful only when depressant poison is cause, 138.

**Paralysis Agitans:**

*conium*, 178.  
*hyoscine*, a useful palliative, 111.

**Paraplegia, Myelitic:**

*phosphorus*, may be of service, 340.  
*silver nitrate*, probably of no value, 317.

**Parturition:**

See LABOR.

**Pemphigus:**

*arsenic*, 351.

**Pericardial Effusions:**

See EFFUSION, PERICARDIAL.

**Pericarditis:**

*mercury*, when exudate is fibrinous, 367.  
*potassium iodide*, in cases with serous effusion, 377.

**Peritonitis:**

*blisters*, 603.  
*iodoform*, in tuberculous peritonitis, 384.  
*mercury*, in sthenic forms of puerperal peritonitis or where fibrinous exudate, 367.  
*opium*, very useful for its antiphlogistic action as well as checking intestinal peristalsis, 65.  
*poultices*, a useful means of applying heat, 629.  
*veratrum*, has been highly praised, its tendency to vomit must be controlled by opium, 265.

**Pernicious Anæmia:**

*iron*, of very little service, 326.

**Pernicious Fever:**

See MALARIA.

**Pertussis:**

See WHOOPING-COUGH.

**Petit Mal:**

*amyl nitrite*, as a diagnostic agent, 168.  
*bromides*, less generally of service than in major epilepsy, 157.  
*chloretone*, 92.

**Phagedæna:**

*nitric acid*, as a caustic, 615.

**Phantom Tumor:**

*Calabar bean*, acts by stimulating intestinal muscles, 151.

**Pharyngitis :**

*suprarenal extract*, to overcome congestion, 245.

**Phenol-Poisoning :**

*treatment of*, 672.

**Phlegmons :**

*ichthargan*, applied in form of ointment, 320.

*phenol*, deep injections of value, 669.

**Phosphatic Gravel :**

*benzoic acid*, 693.

**Phosphaturia :**

*benzoic acid*, to prevent precipitation of phosphates from urinary fermentation, 693.

*glycero-phosphoric acid*, when daily elimination of phosphorus is excessive, 337.

*hexamethylenamine*, as a urinary antiseptic, 557.

**Phosphorus-Poisoning :**

*treatment of*, 344.

**Phthisis :**

*alcohol*, of value as an accessory food and stimulant to digestion, 205.

*antipyrine*, to control the fever, 462.

*arsenic*, in fibroid or slowly progressing types, 351.

*calcium phosphate*, 335.

*camphoric acid*, to check the night-sweats, 192.

*cannabis indica*, as a euthanasiac, 117.

*cantharidin*, (note) 605.

*cocaine*, as a local application in irritated throat conditions, 126.

*codeine*, to check the cough, 72.

*cod-liver oil*, of service on account of food value and perhaps through some specific action, 388.

*creosote*, acts as a stimulant expectorant, 675.

*creosote carbonate*, asserted to be less injurious to the stomach than creosote, 676.

*formaldehyde*, has been employed by inhalation with doubtful benefit, 689.

*gallic acid*, to lessen the night-sweats, 287.

*guaiaicol*, as a stimulant expectorant, 677.

*heroin*, perhaps the most generally useful cough sedative known, 75.

*hypophosphites*, 336.

*iodine*, to be used only in very chronic conditions, 376.

*prunus virginiana*, used for cough, but very feeble, 478.

*sulphuretted hydrogen*, an active but unpleasant expectorant, 578.

*theocol*, 676.

*tuberculin*, its precise value as a curative agent is uncertain, 415.

**Piles :**

See HEMORRHOIDS.

**Pityriasis :**

*oil of cajuput*, 442.

*resorcinol*, 685.

**Pleurisy :**

*atropine*, as a circulatory stimulant in conditions of collapse, 105.

*blisters*, their counter-irritant effect often of service, 603.

*gelsemium*, 173.

*iodine*, in chronic cases with serous effusion, 377.

*mercury*, beneficial in cases with fibrinous exudate, 367.

*potassium iodide*, when serous effusion is present, 377.

*poultices*, the whole chest may be covered, 629.

*salicic acid*, recommended as diuretic in pleural effusion, 452.

**Pleuritic Effusions :**

See EFFUSION, PLEURAL.

**Pneumonia :**

- alcohol*, as a cardiac stimulant, 203.
- antipyrine*, to lessen fever, 462.
- arsenic*, in chronic or fibrous pneumonia, 351.
- atropine*, as a circulatory stimulant, 104.
- blisters*, 603.
- camphor*, used hypodermically is a very useful cardiac stimulant in emergencies, 191.
- cold-water compresses*, preferable to hot applications when temperature is high, 629.
- digitalis*, as heart stimulant, especially valuable in later stages, 231.
- ergot*, used in the early stages, 589.
- gelsemium*, 173.
- guaiacol*, used as antipyretic, but is dangerous, 677.
- mercury*, 367.
- musk*, as a nervous stimulant in adynamic forms, 15.
- naphthol*, oily solution dropped into trachea, 681.
- oil of turpentine*, as a counter-irritant application, 551.
- phosphorus*, for the nerve exhaustion in adynamic cases, 339.
- poultices*, 629.
- tartar emetic*, to reduce circulatory excitement, 260.
- theocol*, 678.
- veratrum viride*, 265.

**Poisoning :**

- alcohol*, as cardiac stimulant, 20
- ammonia*, hypodermically, as circulatory stimulant, 185.
- apomorphine*, as emetic, 642.
- atropine*, as a respiratory and circulatory stimulant, 105.
- ipecacuanha*, as an emetic, 491.
- mustard*, a prompt and efficient but unpleasant emetic, 496.
- potassium permanganate*, antidotal to alkaloids, 660.
- physiological salt solution*, useful to maintain circulation and increase elimination, 526.
- strychnine*, probably most powerful respiratory stimulant known, 140.
- zinc sulphate*, the most generally useful emetic in poisoning, 496.

**Poliomyelitis, Acute :**

See INFANTILE PARALYSIS.

**Polyuria :**

See DIABETES INSIPIDUS.

**Post-partum Hemorrhage :**

- ergot*, acts by causing uterine contractions, most valuable remedy known, 587.
- ipecacuanha*, supposed to affect coagulability of blood, 492.

**Pregnancy :**

- calcium phosphate*, as a prophylactic against foetal rickets, 336.
- cerium oxalate*, for vomiting, 307.
- confection of senna*, useful as a laxative, 507.
- ipecacuanha*, for relief of vomiting, 491.

**Prolapse of Rectum :**

- strychnine*, 139.

**Prurigo :**

- hydrocyanic acid*, a local anæsthetic used to allay itching, 280.
- naphthol*, used in form of soap as antiseptic, 681.

**Pruritus :**

- brucine*, 143.
- glycerin*, when there is lack of sebaceous secretions, 626.
- hydrocyanic acid*, 280.
- menthol*, a useful local anæsthetic, 681.
- tobacco*, 175.



**Prussic Acid poisoning :**

*treatment of*, 281.

**Pseudo-membranous Croup :**

See CROUP.

**Psoriasis :**

*arsenic*, employed internally, 351.

*chrysarobin*, one of the most efficacious remedies known for this disease, 601.

*glycerin*, emollient, is excellent vehicle for more powerful drugs, 626.

*iodine*, of secondary value, 378.

*oil of cajuput*, stimulant and parasiticide, 442.

*phosphorus*, used internally, 340.

*pyrogallol*, dangerous if used too freely, 616.

*resorcinol*, 685.

*thymol iodide*, 387.

*thyroid extract*, claimed to have a peculiar alterative effect on skin, 406.

**Psorophthalmia :**

*citrine ointment*, 371.

**Ptyalism :**

*atropine*, the most valuable internal remedy known, 105.

*tannic acid*, used in solution as mouth wash, 286.

**Puerperal Convulsions :**

*amyl nitrite*, if used immediately after labor may cause post-partum hemorrhage, 168.

*anæsthetics*, 22.

*camphor*, of little value, 191.

*chloral*, one of the most powerful anticonvulsants known, 80.

*ethyl carbamate*, as an anticonvulsant, 89.

*veratrum*, 265.

**Puerperal Eclampsia :**

See PUERPERAL CONVULSIONS.

**Puerperal Fever :**

*digitalis*, as a circulatory stimulant, 231.

*nuclein*, claimed to prevent the growth of septic bacteria, 402.

*oil of turpentine*, may be used both internally and externally, 551.

*streptococcus antitoxin*, results have not proved encouraging, 410.

See also SEPTICÆMIA.

**Purpura Hæmorrhagica :**

*gelatin*, acts by increasing coagulability of blood, 401.

*oil of turpentine*, 551.

**Pyemia :**

*alcohol*, as a circulatory and general stimulant, 203.

*quinine*, not probable that it exercises any direct action on pyogenic organisms, 428.

*tincture of ferric chloride*, 328.

**Pyelitis :**

*buchu*, a mild stimulant to the urinary mucous membranes, 546.

*cantharides*, actively stimulating, to be used only in chronic cases, 605.

*copaiba*, 553.

*juniper*, diuretic and stimulating, used in chronic cases, 555.

*methylene-blue*, doubtful if of value, 439.

*salicylic acid*, acts as urinary antiseptic, 452.

*turpentine*, 551.

*urotropin*, urinary antiseptic, especially useful in lithemic patients, 557.

*uva ursi*, mildly astringent and diuretic, 547.

**Pyrexia :**

See FEVER.

**Pyrosis :**

*bismuth*, antiseptic and sedative, 306.  
*manganese dioxide*, 329.

**Quinsy :**

*salicylates*, 452.

**Rachitis :**

See RICKETS.

**Remittent Fever :**

*arsenic*, used only when quinine not available, 350.  
*diaphoretics*, when paroxysms are close together, 561.  
*quinine*, must be used in full dose, 430.  
*Warburg's tincture*, a very powerful combination containing quinine, 436.

**Renal Calculi :**

See CALCULI.

**Retention of Urine :**

*strychnine*, when due to atony of bladder, 139.

**Retina, Detachment of :**

*dionine*, 74.

**Retinitis :**

*iodipin*, 380.

**Rheumatic Neuralgia :**

*aconite*, applied locally, 273.  
*potassium iodide*, in subacute or chronic cases, 376.  
*salicylates*, the most generally serviceable remedy, 451.

**Rheumatism :**

*aconite*, used to produce sweat, 273.  
*arsenic*, in chronic cases; may be alternated with iodides, 352.  
*aspirin*, a form of exhibiting salicylic acid much less likely to disturb digestion, 456.  
*Burgundy pitch*, as a mildly counter-irritant plaster, 610.  
*carbolic acid injections*, 838.  
*cathartics*, 500.  
*cod-liver oil*, useful in chronic types especially when poor nutrition, 390.  
*colchicum*, in those cases approaching the gouty type, 393.  
*diaphoretics*, to prevent muscular rheumatism following exposure, 561.  
*Donovan's solution*, used only in chronic cases, 371.  
*guaiac*, 397.  
*ichthyol*, mildly counter-irritant and alterative, 396.  
*iodine*, used externally in chronic cases, 377.  
*iodoform*, internally in chronic cases as analgesic, 376.  
*jaborandi*, to produce sweating, 567.  
*magnesia*, antacid and laxative, 635.  
*methylene-blue*, as an analgesic, 438.  
*oil of cajuput*, 442.  
*phenocoll hydrochloride*, 472.  
*phenol*, injected deeply, 669.  
*potassium salts*, antacid and increase oxidation, especially valuable in acute cases, 538.  
*potassium iodide*, a very valuable remedy in chronic cases, 376.  
*pyramidon*, in acute cases to relieve pain, 478.  
*quinine salicylate*, 430.  
*salicylates*, the standard remedies in all forms of rheumatism, 451.

**Rheumatism (Continued):**

- salipyrin*, as an analgesic, 472.
- salol*, not very powerful but often of service in chronic cases, 673.
- salophen*, acts much like salol, 457.
- sulphur*, as a laxative, also as alterative in chronic cases, 694.
- water*, aids elimination of noxious materials, 526.
- xanthoxylum*, 398.

**Rheumatism, Inflammatory:**

- antipyrine*, to relieve excessive fever, 462.
- benzoic acid*, asserted to be equal to salicylic acid, 692.
- cimicifuga*, an old remedy rarely employed to-day, 19
- lemon-juice*, 513.
- phenocoll hydrochloride*, 472.
- potassium salts*, one of most valuable treatments; encourages oxidation and corrects systemic hyperacidity, 538.
- quinine*, in very large doses, efficacious but dangerous, 429.
- salicylic acid*, relieves pain and hyperpyrexia and probably has direct curative effect on morbid metabolism, 451.

**Rheumatoid Arthritis:**

- arsenic*, probably the most frequently useful remedy known, 352.
- potassium iodide*, 376.
- salicylic acid*, but rarely of service, 451.

**Rhinitis:**

- boric acid*, sedative and antiseptic local application, 698.
  - camphor-menthol*, applied locally dissolved in liquid petrolatum, 682.
  - hydrastis*, an excellent local remedy especially in chronic catarrhs, 595.
  - ichthargan*, actively germicidal, may be used in spray, 320.
  - suprarenal extract*, constricts the engorged blood-vessels, 245.
- See also CATARRH.

**Rhus-Toxicodendron Poisoning:**

- lobelia*, 171.

**Rickets:**

- calcium phosphates*, when there is a deficiency of lime salts in nutriment, 335.
- cod-liver oil*, a valuable remedy especially in poorly nourished subjects, 390.
- phosphorus*, stimulates the growth of bone, 340.

**Rigidity of Os Uteri:**

- belladonna*, applied locally, 104.

**Round-Worms:**

- azedarach*, used but comparatively little, 647.
- chenopodium*, a useful remedy, 643.
- oil of turpentine*, 646.
- santonin*, one of the most active drugs against this parasite, 640.
- spigelia*, safe and efficient, 643.

**Salivation:**

- See PTYALISM.

**Scabies:**

- glycerin*, as an emollient vehicle, 626.
- resorcinol*, somewhat antiseptic, 685.
- sulphur*, the most frequently employed remedy, 694.

**Scarlet Fever:**

- alcohol*, as a circulating stimulant for threatened collapse, 203.
- ammonia*, rapidly acting cardiac stimulant, 185.
- antipyrine*, to reduce hyperpyrexia, 462.
- atropine*, has no specific action, as formerly believed, but is valuable as a stimulant,



**Scarlet Fever (Continued) :**

*capsicum*, as a local application for the accompanying sore throat, 483.  
*hydrogen dioxide*, used as antiseptic application to the throat, 662.  
*streptococcus antitoxin*, for secondary infections, especially of throat, 444.  
*urotropin*, probably of use as preventive of nephritis, 557.

**Sciatica :**

*acetopyrin*, as an analgesic, 466.  
*guaiaac*, 529.  
*iodides*, of value in subacute rheumatic cases, 376.  
*salicylates*, the most useful remedy in rheumatic cases, 451.  
*saloquinine*, analgesic and antirheumatic, 437.

**Scleritis :**

*iodipin*, 380.  
*physostigmine*, 152.

**Scleroderma :**

*thiosinamine*, 398.

**Scrofulosis :**

*alcohol*, as an accessory food, 205.  
*calcium phosphate*, 334.  
*calx sulphurata*, internal remedy for scrofulous glands, 694.  
*cod-liver oil*, to improve nutritive condition, 390.  
*gold and sodium chloride*, 373.  
*gold oxide*, 373.  
*ichthalbin*, a derivative of ichthylol suitable for internal use, 396.  
*iodine*, used internally for glandular enlargements, especially when no suppuration, 378.  
*phosphoric acid*, largely used but of little value, 334.  
*syrup of ferrous iodide*, combines alterative action of iodine with tonic effect of iron, 328.

**Scurvy :**

*lemon-juice*, a specific; the only remedy of value, 513.

**Seat-Worms :**

*forced enemata*, 501.  
*naphthalin*, given by injection, 680.  
*quassia*, probably the most generally useful remedy; use in enema, 476.  
*vinegar*, 290.

**Seborrhœa :**

*arsenic*, internally when of neurotic origin, 351.  
*glycerin*, externally to soften the skin, 626.  
*resorcin*, stimulant and antiseptic, 685.

**Seminal Emissions :**

See SPERMATORRHŒA.

**Septicæmia :**

*antitoxin*, has not given brilliant results, 410.  
*colloidal silver*, its value is problematical, 320.  
*formaldehyde*, intravenous injections of no service, 690.  
*ichthargan*, used hypodermically, but no positive evidence of value, 320.  
*quinine*, perhaps useful as antipyretic, has no specific action, 428.

**Serous Diarrhœa :**

See DIARRHŒA.

**Sexual Excitement :**

*camphor*, a feeble sedative, 191.  
*hops*, frequently employed but of little use, 18.  
*hyoscine hydrobromate*, one of the most reliable sedatives known for this condition, 111.

**Sexual Excitement (Continued):**

*monobromated camphor*, 161.  
*potassium bromide*, a very valuable remedy, 158.  
 See also NYMPHOMANIA.

**Shock:**

See COLLAPSE.

**Sick Headache:**

*antacids*, to correct acidity of stomach, 632.  
*aromatic spirit of ammonia*, the most generally useful antacid, 632.  
*magnesia*, laxative and antacid, 635.

**Sick Stomach:**

*creosote*, local anæsthetic and antiseptic, 675.  
*ipecacuanha*, as a gastric stimulant in atonic nausea, 491.  
 See also VOMITING.

**Silver-Nitrate Poisoning:**

*treatment of*, 318.

**Singultus:**

See HICCOUGH.

**Sinking-Spells:**

See SYNCOPE.

**Skin Diseases:**

*aluminum hydroxide*, mildly astringent, 292.  
*arsenic*, used internally in chronic conditions, 351.  
*chalk*, as a protective and desiccant, 637.  
*chrysarobin*, an excellent stimulating application, especially in psoriasis, 601.  
*citrine ointment*, 371.  
*cod-liver oil*, used internally to improve nutrition, 390.  
*Donovan's solution*, used internally as an alterative, 371.  
*gold iodide*, 373.  
*ichthyol*, a local remedy of wide applicability, 396.  
*iodine*, occasionally used as an antiseptic, 378.  
*magnesia*, as a laxative antacid, 635.  
*naphtol*, as an antiseptic soap, 681.  
*nitro-hydrochloric acid*, for its stomachic effect, 333.  
*oil of cajuput*, stimulating and parasiticide, 442.  
*ointment of oxide of mercury*, 371.  
*ointment of zinc oxide*, 309.  
*phosphorus*, internally in various chronic conditions, 340.  
*resorcinol*, 685.  
*salicylic acid*, 454.  
*sulphur*, used both internally and externally, 694.  
*tar*, 576.  
*thyroid extract*, especially in psoriasis and keloid, 406.  
*vinegar*, as a sedative astringent in acute inflammations, 290.  
*zinc oxide*, a widely useful astringent, 308.

**Sleeplessness:**

*bromipin*, a preparation of bromides, 160.  
*bromolein*, 160.  
*cannabis indica*, 117.  
*chloral*, the most powerful hypnotic known in nervous insomnia, 79.  
*chloralformamid*, less powerful but less depressant than chloral, 90.  
*chloralose*, uncertain in its effects, 91.  
*chloretone*, feeble and uncertain, 92.  
*dormiol*, of moderate power in insomnia of nervous origin, 90.  
*hedonal*, sometimes of use in cases of not great severity nor associated with pain, 90.  
*hyoscine hydrobromide*, especially serviceable in insomnia of insanity or delirium, 110.

**Sleeplessness (Continued):**

- isopral*, as actively depressant as chloral hydrate, over which it has no advantages, 90.
- opium*, chiefly of value in insomnia due to pain, 64.
- paraldehyde*, a safe and powerful remedy in sleeplessness not associated with pain, 88.
- potassium bromide*, comparatively feeble as direct somnifacient, but useful in cases where wakefulness is caused by stimuli from without, 157.
- sulphones*, including sulphonal and trional valuable in nervous insomnias, 84.
- urethan*, a safe and moderately active remedy in nervous insomnia, 89.
- veronal*, 91.

**Smallpox :**

- ichthyol*, employed locally to prevent pitting, 396.
- opium*, to sustain system by blunting sensibilities, 65.
- thiosinamine*, to cure the scars after smallpox, 398.

**Snake-poisoning :**

- alcohol*, of value as circulatory stimulant, but is not a specific as sometimes believed, 204.
- ammonia*, a useful heart stimulant, inject hypodermically, 185.
- antitoxin*, acts specifically in bites from certain varieties of snakes, 413.
- potassium permanganate*, as a local antidote; should be injected into wound, 660.

**Sore Nipples :**

- See NIPPLES, SORE.

**Sore Throat :**

- acacia*, dissolved in the mouth is very soothing in acute inflammations, 617.
- alum*, as an astringent, not fitted for gargle, 292.
- carbolic acid*, in ulcerated or diphtheritic sore throat as an antiseptic, 669.
- chlorine water*, as a disinfectant gargle in violent infections, 659.
- cocaine*, applied locally as vasoconstrictor and anæsthetic, 126.
- creosote*, locally as antiseptic, 676.
- mercury*, internally as antiphlogistic, 367.
- phenol injections*, 669.
- potassium chlorate*, a very valuable astringent in not too acute inflammations, 541.
- salicylates*, specific in tonsilitis and rheumatic angina, 452.
- silver nitrate*, sedative astringent and germicidal, 316.
- sumach berries*, make an excellent astringent gargle, 288.
- tannic acid*, applied by swab or as a gargle, 286.
- thymol*, as antiseptic, 683.

**Spasms :**

- aconite*, not generally useful, 273.
- amyl nitrite*, a very powerful and rapidly acting but fugacious relaxant, 167.
- anæsthetics*, in severe hysterical or spinal convulsions, 22.
- asafetida*, when due to hysteria, 17.
- atropine*, in local spasms especially of involuntary muscles, 104.
- chloral*, in all forms of violent generalized convulsions a valuable remedy, 80.
- hyoscine*, in asthma, whooping-cough, and similar disorders, 111.
- lobelia*, in spasms of the bronchial muscles, 171.
- oil of cajuput*, recommended in intestinal spasm, 442.
- opium*, especially in cerebral or painful spasms, 64.
- potassium bromide*, one of the most valuable remedies in spinal and epileptic convulsion, 157.
- sulphonal*, a feeble anticonvulsant, 84.

**Spermatorrhœa :**

- antipyrine*, 463.
- chloral*, useful in spasmodic types, 80.
- digitalis*, asserted to be actively anaphrodisiac, 232.
- hyoscine hydrobromide*, one of the most valuable remedies known, 111.
- monobromated camphor*, 161.
- potassium bromide*, a very useful sexual sedative, 157.
- sulphonal*, 84.
- turpentine*, in cases with marked atony, 551.



**Spinal Congestion :**

*ergot*, 589.

**Spinal Depression :**

*strychnine*, 138.

**Spinal Scleroses :**

*gold and sodium chloride*, beneficial results have been claimed for it, 373.  
*silver nitrate*, an old remedy of doubtful value, 317.

**Spleen, Enlargement of :**

*ergot*, contracts vessels, useful in cases of chronic congestion, 589.  
*potassium bromide*, in post-malarial spleens, 158.

**Spongy Gums :**

*tannic acid*, 286.

**Sprains :**

*arnica*, as a stimulant application, 610.  
*camphor*, as a counter-irritant, 191.  
*dilute acetic acid*, a sedative, astringent lotion, 290.  
*ichthyol*, 396.  
*lead water*, a frequently employed sedative embrocation, 294.

**Status Epilepticus :**

*amyl nitrite*, 167

**Stomach, Diseases of :**

See CANCER OF STOMACH, DYSPEPSIA GASTRITIS etc.

**Stomatitis :**

*boric acid*, a large crystal of borax allowed to dissolve in the mouth is an excellent treatment, 698.  
*phenol*, the ulcers to be touched with a concentrated solution in glycerin, 669.  
*potassium chlorate*, employed both as a mouth wash and taken internally, 541.  
*sodium chlorate*, (note) 541.  
*thymol*, useful as antiseptic on account of pleasant taste, 683.

**Stricture :**

*anæsthetics*, in spasmodic stricture of œsophagus, 22.  
*belladonna*, in spasmodic stricture of either urethra or bowels, 104.  
*thiosinamine*, asserted to be useful in true urethral stricture, 398.

**Strychnine-Poisoning :**

*amyl nitrite*, use by inhalation or hypodermically to produce immediate relaxation, 168.  
*bromides*, among the most valuable remedies we have, 157.  
*chloral*, a very useful spinal depressant, 80.  
*physiological salt solution*, to aid in elimination of poison, 527.  
*physostigma*, a remedy of only secondary power, 151  
*treatment of*, 142.

**Suffocative Catarrh :**

*apomorphine hydrochlorate*, as an emetic to evacuate exudate, 495.  
*treatment of asphyxia in*, 571.

**Sulphone-Poisoning :**

*treatment of*, 87.

**Summer Complaint :**

See CHOLERA INFANTUM.

**Sunburn :**

*dilute acetic acid*, a valuable sedative astringent, 290.

**Suppressed Menstruation :**

See AMENORRHEA.

**Suppression of Urine :**

*calomel*, one of the most powerful diuretics known in parenchymatous nephritis, 531.

*jaborandi*, given in small doses sometimes of service, 567.

water, when suppression dependent on acute irritation of kidneys, 526

**Sweating, Excessive :**

See HYPERIDROSIS.

**Sycosis :**

*opsonic treatment*, 415.

**Syncope :**

*alcohol*, a rapidly acting cardiac stimulant, 204.

*amonnia*, irritant action of vapors on mucous membrane of nose acts reflexly as stimulant, 185.

*amyl nitrite*, a dangerous remedy, as the slightest overdose is depressant, 168.

*digitalis*, give hypodermically in large doses, 230.

*ether*, 30.

**Synovitis :**

*phenol injections*, 669

**Syphilis :**

*berberis*, 477.

*calcium phosphate*, recommended in syphilitic periostitis, also in gumma, 336.

*cod-liver oil*, in the cachexia of tertiary stage, 390.

*copper sulphate*, as adjunct to mercury, 310.

*difluor-diphenyl*, as a local application to ulcerating lesions, 659.

*gold and sodium chloride*, in sclerosis of nervous system, 373.

*gold iodide*, 373.

*guaiac*, a remedy of secondary importance, may be used as adjunct, 397.

*ichthalbin*, 396.

*iodipin*, has same effect as iodides, but acts more slowly and persistently, 380.

*iodoform*, used internally especially when "night-pains," 382.

*iodol*, 386.

*mercury*, especially useful in early stages, but a specific in all forms, 367.

*nitric acid*, 332.

*nitro-hydrochloric acid*, to improve digestion, 333.

*potassium iodide*, a specific, employed most frequently in tertiary stage, 376.

*sarsaparilla*, perhaps of service as adjunct, 397.

*sulphur*, natural sulphur-waters, recommended in chronic syphilis, 694.

*thiosinamine*, as a local application in syphilitic skin lesions, 398.

*thymol iodide*, as a dusting powder for local lesions, 387.

**Tapeworm :**

*aspidium*, one of the best remedies against tapeworm, but is poisonous, 645.

*chloroform*, probably of little value, 34.

*cusso*, efficient and harmless, 645.

*ether*, of only secondary value, 30.

*kamala*, 647.

*large enemata*, 501.

*oil of chenopodium*, an active anthelmintic, 643.

*oil of turpentine*, 646.

*pepo*, the safest and one of the most powerful tænicides, 645.

*pomegranate*, efficient, but poisonous in overdose, 646.

*thymol*, 646.

**Tetanus :**

*amyl nitrite*, to allay spasm which threatens immediate death, although powerful too fugacious for constant use, 168.

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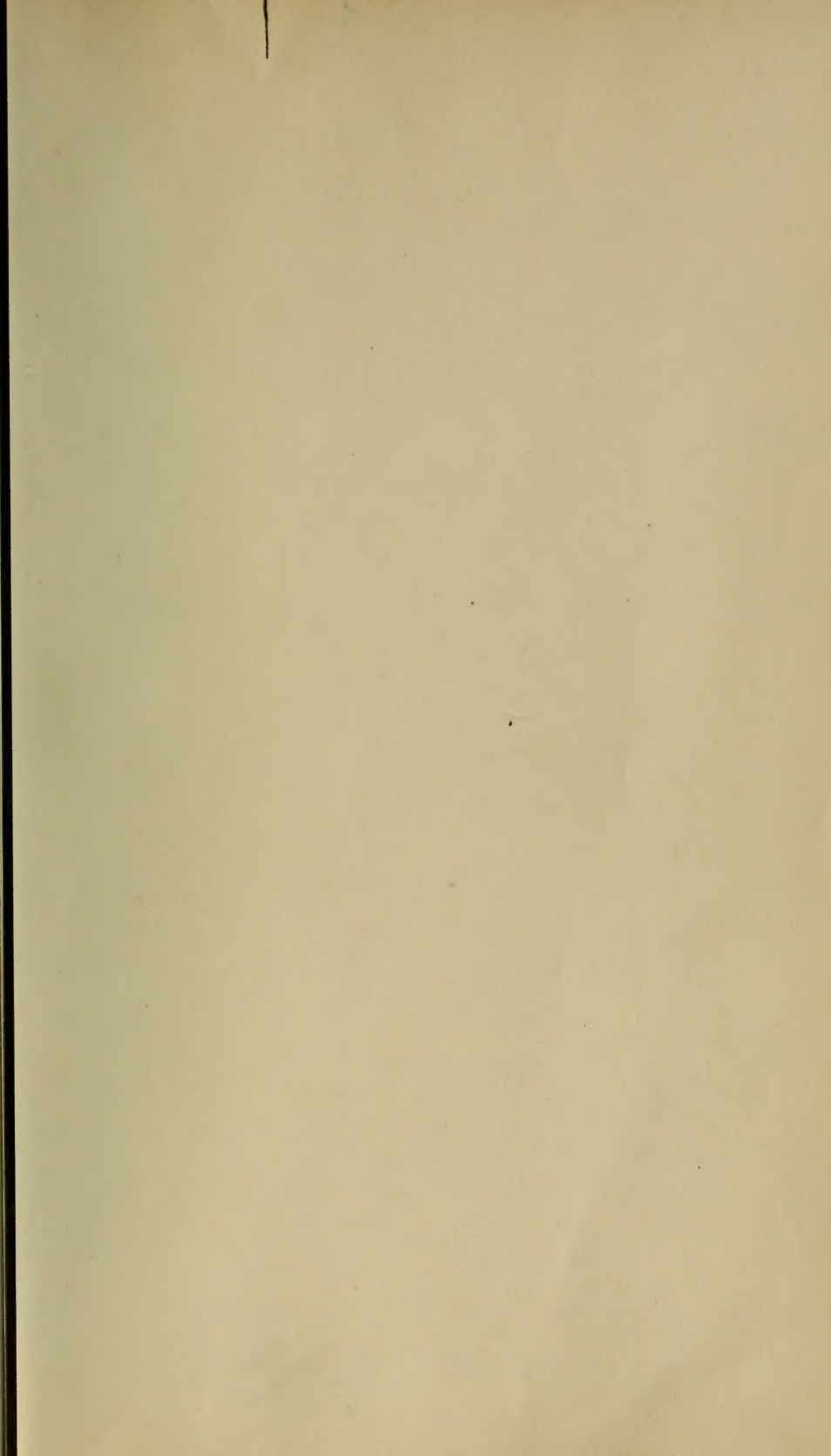
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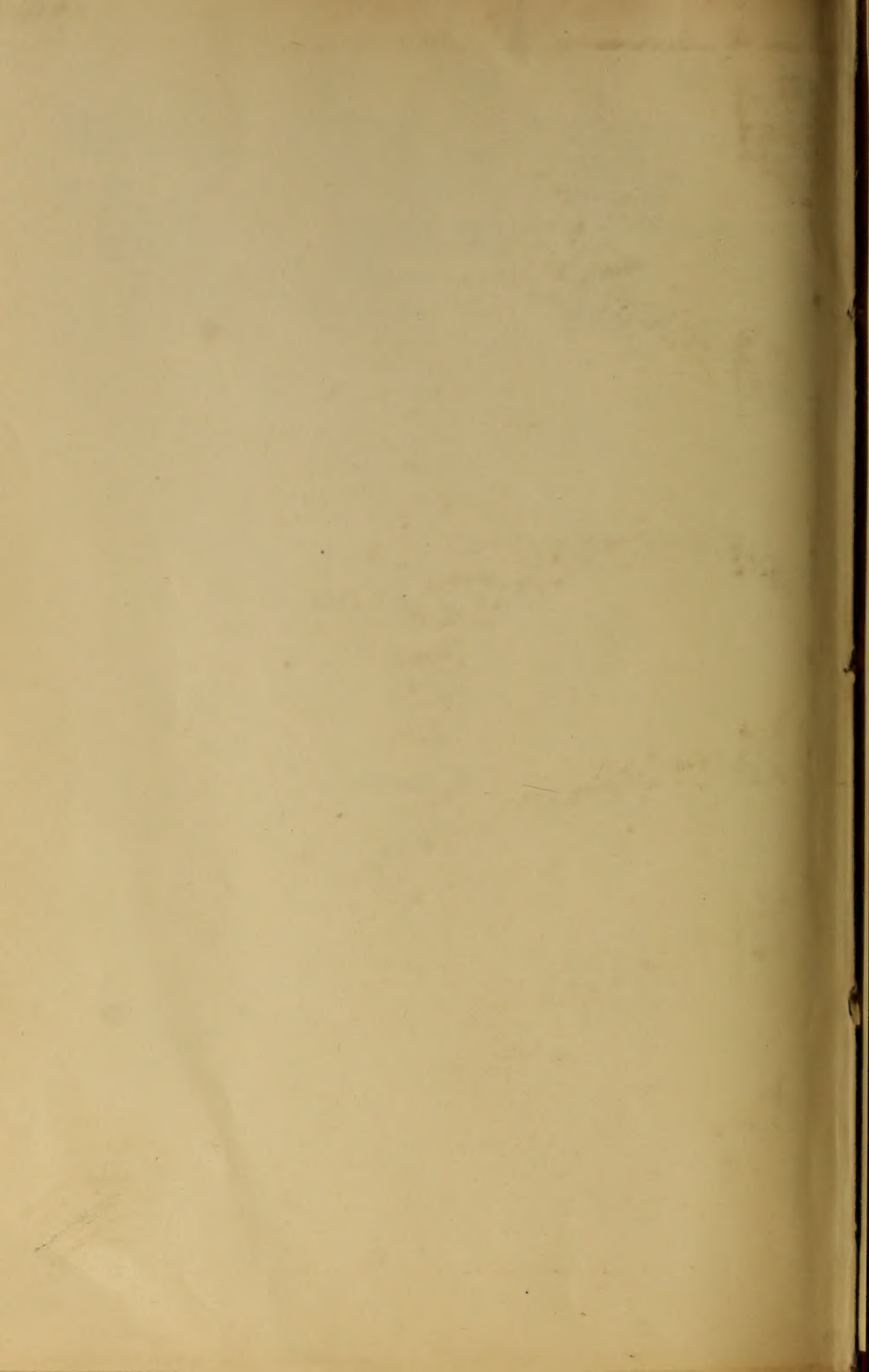
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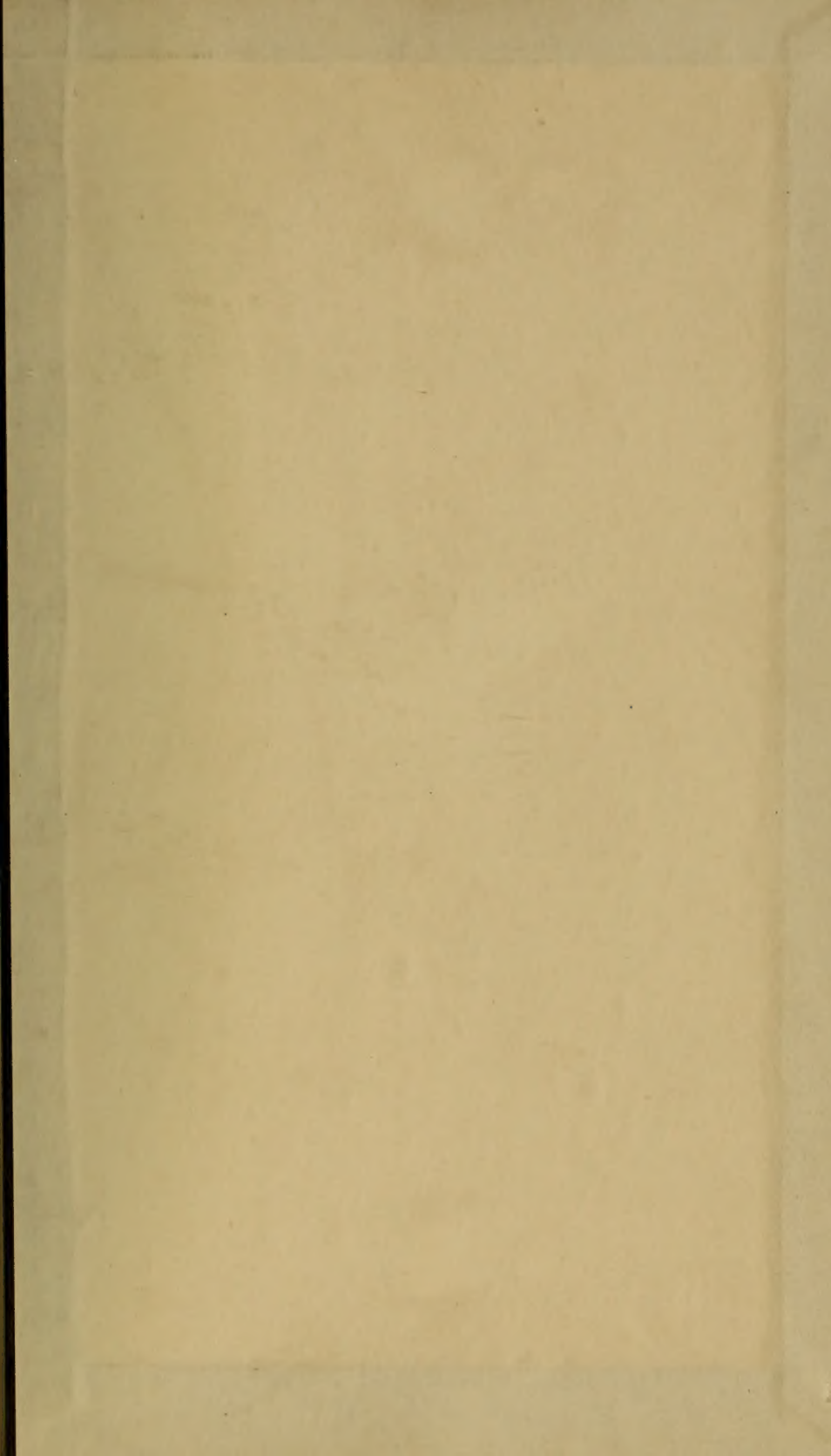
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